Driving biology: The effect of standardized wound management on wound biomarker profiles

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BACKGROUND: The timing of coverage of an open wound is based on heavily on clinical gestalt. DoD's Surgical Critical Care Initiative created a clinical decision support tool that predicts wound closure success using clinical and biomarker data. The military uses a regimented protocol consisting of serial washouts and debridements. While decisions around wound closure in civilian centers are subject to the same clinical parameters, preclosure wound management is, generally, much more variable. We hypothesized that the variability in management would affect local biomarker expression within these patients.

METHODS: We compared data from 116 wounds in 73 military patients (MP) to similar data from 88 wounds in 78 civilian patients (CP). We used Wilcoxon rank-sum tests to assess concentrations of 32 individual biomarkers taken from wound effluent. Along with differences in the debridement frequency, we focused on these local biomarkers in MP and CP at both the first washout and the washout performed just prior to attempted closure.

RESULTS: On average, CP waited longer from the time of injury to closure (21.9 days, vs. 11.6 days, $p < 0.0001$) but had a similar number of washouts (3.86 vs. 3.44, $p = 0.52$). When comparing the wound effluent between the two populations, they had marked biochemical differences both when comparing the results at the first washout and at the time of closure. However, in a subset of civilian patients whose average number of days between washouts was never more than 72 hours, these differences ceased to be significant for most variables.

CONCLUSION: There were significant differences in the baseline biochemical makeup of wounds in the CP and MP. These differences could be eliminated if both were treated under similar wound care paradigms. Variations in therapy affect not only outcomes but also the actual biochemical makeup of wounds. (*J Trauma Acute Care Surg.* 2020;88: 379–389. Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.)

LEVEL OF EVIDENCE: Therapeutic, level IV.

KEY WORDS: Precision medicine; wound management; biomarkers.

Both civilian and military trauma surgeons are often called upon to manage complex wounds, and these wounds create a significant burden to both patients and the health care system. Indeed, recent military conflicts have created a heightened awareness of the need and benefit of standardized wound care paradigms as military surgeons have increasingly been faced with massive soft tissue injuries.[1] These challenges have led to the development of strict guidelines around the management of wounds in military hospitals and the desire to more precisely predict the outcome of wound coverage strategies in these settings.[1,2] Specifically, there have been extensive efforts by military surgeons to create a clinical decision support tool (CDST) designed to predict the success of attempts at wound coverage.[3] These efforts have led to the creation of WounDx, a wound coverage CDST, which uniquely combines administrative, clinical, and biological analyte–based data to produce a prognostic assessment. This tool has been shown to accurately predict wound healing outcomes in patients managed using the military wound management guidelines.[3,4]

Civilian surgeons are oftentimes called upon to deal with similarly complex wounds in civilian trauma centers. In these centers, however, the broader missions of civilian programs oftentimes compete for resources, such as operative time, and the comorbidities encountered in civilian populations are more varied. These two factors, and others, influence the variability in wound care. Different services have significant differences in philosophy in terms of the frequency and number of operative washouts, types of wound coverage, and variable use of negative pressure and other types of dressings. When this is combined with a more heterogenous patient population, in terms of age and health status, it is unlikely that a tool designed in a military setting with a relatively strict wound management paradigm will translate easily into the civilian setting. The Surgical Critical Care Initiative, a civilian/military, multiinstitutional collaborative has formed in recent years with the overarching goal to create CDSTs in the critical care arena designed to assist clinicians with bedside decision making and to move precision and individualized medicine in the intensive care unit forward.[5]

Because of the need to better understand how a military wound management CDST would translate to the civilian setting, we examined wound effluent and clinical factors from patients being cared for in a major urban civilian trauma center and compared those results to wounds cared for in military centers. Based on our initial results, we hypothesize that variability in wound management affects both patient biology and the accuracy of WounDx when applied to a civilian population, with a secondary hypothesis that frequency of operative washouts contributes to differences in wound effluent biomarker levels in both military and civilian populations. Understanding the biological and clinical differences in these patients will inform creation of a common CDST for guiding wound closure strategies in both populations.

METHODS

Patients were enrolled prospectively after being admitted to the trauma service of a participating institution with an extremity wound of 75 cm^2 or greater. Military patients (MP) were enrolled from Walter Reed National Military Medical Center (WRNMMC) in Bethesda, MD and civilian patients (CP) from

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TABLE 1. Characteristics of the Military and Civilian Populations

Demographics	Military Population (n = 73)	Civilian Population (n = 83)	Civilian Subset With Military-Like Wound Washout Schedule (n = 14)	Civilian Subset Without Military-Like Wound Washout Schedule (n = 69)
Gender	73/73 male (100%)	65/83 male (78.3%)***	10/14 male (71.4%)***	55/69 male (79.7%)***
Age (yrs)	23.3 (18–42)	37.8 (19–80)***	35.5 (24–54)***	38.3 (19–80)***
Race				
African American	3/73 (4.1%)	45/83 (54.2%)***	7/14 (50.0%)***	38/69 (55.1%)***
Asian	2/73 (2.7%)			
Caucasian	60/73 (82.2%)	32/83 (38.6%)***	6/14 (42.9%)***	26/69 (37.7%)***
Latino	8/73 (11.0%)	5/83 (6.0%)***	1/14 (7.1%)***	4/69 (5.8%)***
Other		1/83 (1.2%)***		1/69 (1.4%)***
BMI	25.1 (17.7–35.9)	31.3 (16–67)*** (77 patients with data)	28.5 (21–44)* (13 patients with data)	31.9 (16–67)*** (64 patients with data)
Diabetes	No information	7/71 (9.9%)	2/13 (15.4%)	5/58 (8.6%)
Tobacco Use				
Yes	27/73 (37.0%)	34/75 (45.3%)	5/11 (45.5%)	29/64 (45.3%)
No	46/73 (63.0%)	41/75 (54.7%)	6/11 (54.5%)	35/64 (45.3%)
ISS	19.6 (8–59)	13.5 (0–50)***	18.2 (4–41)	12.6 (0–50)***
Injury Mechanism				
Blast Injury	63/73 (86.3%)	N/A	N/A	N/A
Gunshot Wound	9/73 (12.3%)	21/83 (25.3%)***	1/14 (7.1%)***	20/69 (29.0%)***
Crush Injury	1/73 (1.4%)	5/83 (6.0%)***	N/A	5/69 (7.2%)***
Motor Vehicle Accident	N/A	48/83 (57.8%)***	11/14 (78.6%)***	37/69 (53.6%)***
Blunt Trauma	N/A	7/83 (8.4%)***	2/14 (14.3%)***	5/69 (7.2%)***
Compartment Syndrome	N/A	1/83 (1.2%)***	N/A	1/69 (1.4%)***
Burn Injury	N/A	1/83 (1.2%)***	N/A	1/69 (1.4%)***
Number of Operations	6.5 (3–16)	2.6 (0–12)***	2.4 (1–5)***	2.6 (0–12)***
Blood Products at Initial Resuscitation (first 24 hrs) in units	22.2 (0–420)	8.7 (0–97)*	7.9 (0–65)	8.9 (0–97)*
Blood Products Total in units	35.1 (0–519)	14.4 (0–134)**	13.2 (0–81)	14.7 (0–134)**
Presence of Vascular Injury	40/73 (54.8%)	37/83 (44.6%)	8/14 (57.1%)	29/69 (42.0%)
Arterial Vascular Injury				
Central Abdomen	1/73 (1.4%)	1/83 (1.2%)		1/69 (1.4%)
Central Thorax	2/73 (2.7%)	1/83 (1.2%)		1/69 (1.4%)
Peripheral Extremity	44/73 (60.3%)	29/83 (34.9%)**	8/14 (57.1%)	21/69 (30.4%)***
Venous Vascular Injury				
Central Abdomen		2/83 (2.4%)		2/69 (2.9%)
Peripheral Extremity	41/73 (56.%)	18/83 (21.7%)***	3/14 (21.4%)*	15/69 (21.7%)***
Hospital Length of Stay in days	34.6 (8–406)	30.1 (2–159)	22.8 (11–45)	31.6 (2–159)
Intensive Care Unit Length of Stay in days	5.4 (2–12)	8.2 (0–77)	6.6 (0–31)	8.6 (0–77)
Death	0/73 (0%)	0/83 (0%)	0/14 (0%)	0/69 (0%)
Time from Injury to Admission in days	5 (2–12)	4.7 (0–26)	4.4 (2–12)	4.8 (0–26)
Wound Management	Military Population Wounds (n = 116)	Civilian Population Wounds (n = 110)	Civilian Subset Wounds with Military-like Wound Washout Schedule (n = 16)	Civilian Subset Wounds without Military-like Wound Washout Schedule (n = 94)
Wound closure type				
Primary closure	78/116 (67.2%)	33/95 (34.7%)***	5/15 (33.3%)***	28/80 (35.0%)***
Skin grafting	16/116 (13.8%)	55/95 (57.9%)***	7/15 (46.7%)***	48/80 (60.0%)***
Complex closure (e.g., rotational flap, free flap)	4/116 (3.4%)	7/95 (7.4%)***	3/15 (20.0%)***	4/80 (5.0%)***
Integra Matrix wound dressing	18/116 (15.5%)			
Wound type				
STI	33/116 (28.4%)	89/110 (80.9%)***	13/16 (81.2%)***	76/94 (80.8%)***
Open fracture	22/116 (19.0%)	2/110 (1.8%)***	0/16 (0.0%)***	2/94 (2.1%)***
Amputation	61/116 (52.6%)	19/110 (17.3%)***	3/16 (18.8%)***	16/94 (17.0%)***

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TABLE 1. *(Continued)*

Demographics	Military Population (n = 73)	Civilian Population (n = 83)	Civilian Subset With Military-Like Wound Washout Schedule (n = 14)	Civilian Subset Without Military-Like Wound Washout Schedule (n = 69)
Bacteremia (presence of bacteria in blood detected at any point)	33/116 (28.4%)	No information	No information	No information
CFU/g tissue for organisms detected by quantitative microbial culture	5.746e+06 (0-1e+08) (108 wounds with data)	No information	No information	No information
CFU/mL of effluent for organisms detected by quantitative microbial culture	1.442e+06 (0-4.6e+07) (95 wounds with data)	No information	No information	No information
Wound location				
Left lower extremity	51/116 (44.0%)	61/104 (58.7%)	9/16 (56.2%)	52/88 (59.1%)
Right lower extremity	46/116 (39.7%)	32/104 (30.8%)	6/16 (37.5%)	26/88 (29.5%)
Left upper extremity	9/116 (7.8%)	5/104 (4.8%)	0/16 (0.0%)	5/88 (5.7%)
Right upper extremity	10/116 (8.6%)	6/104 (5.8%)	1/16 (6.2%)	5/88 (5.7%)
Wound length, cm	22.5 (6–53)	23.5 (0–50) (37 wounds with data)	21.5 (15–37) (4 wounds with data)	23.7 (0–50) (33 wounds with data)
Wound width, cm	12.7 (3–37)	10 (0–30)** (38 wounds with data)	10 (8–12) (4 wounds with data)	10 (0–30)** (34 wounds with data)
Wound depth, cm	5.6 (0.5–45)	1.6 (0–11)*** (49 wounds with data)	1.2 (0–5)*** (9 wounds with data)	1.7 (0–11)*** (40 wounds with data)
Wound area, cm^2	240 (25.1–1729.2) (115 wounds with data)	290.4 (0–1500) (32 wounds with data)	233.3 (120–444) (3 wounds with data)	296.2 (0–1500) (29 wounds with data)
Time from injury to wound closure in days	11.6 (5–43)	21.9 (4–89)***	10.6 (6–18)	23.9 (4–89)***
Wound outcome				
Healed	90/116 (77.6%)	81/104 (77.9%)	12/16 (75.0%)	69/88 (78.4%)
Dehisced	26/116 (22.4%)	23/104 (22.1%)	4/16 (25.0%)	19/88 (21.6%)

Asterisks indicate a statistically significant difference ($p < 0.05$) compared to the military population (Fisher tests for categorical data and Wilcoxon rank-sum tests for continuous data). Statistically significant differences are coded as "*" for $p < 0.05$, "**" for $p < 0.01$, and "***" for $p < 0.001$.

For categorical data, proportions are reported with percentages in parentheses. For continuous data, means are reported with ranges (min-max) in parentheses.

Complete information for every variable was not always available. For categorical variables, the denominators of the proportions indicate the number of samples with complete data. For continuous variables, the number of samples with complete data is indicated.

CFU, colony-forming unit.

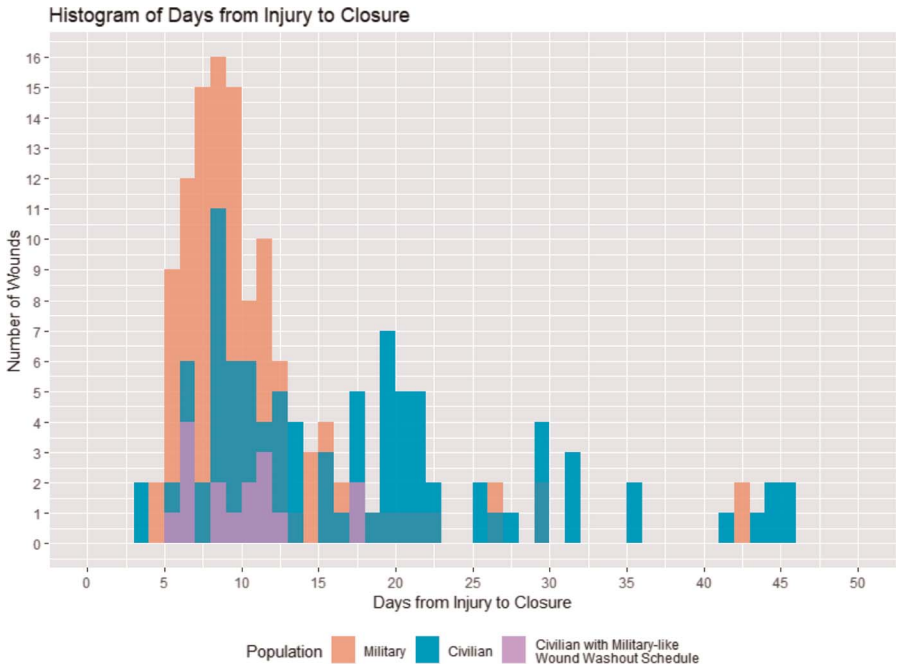

Figure 1. Histogram of days from injury to closure for the civilian population and military population. The mean from injury to closure for the civilian population was 21.9 days. The mean from injury to closure for the military population was 11.6 days. The median from injury to closure for the civilian population was 17.5 days. The median from injury to closure for the military population was 10 days.

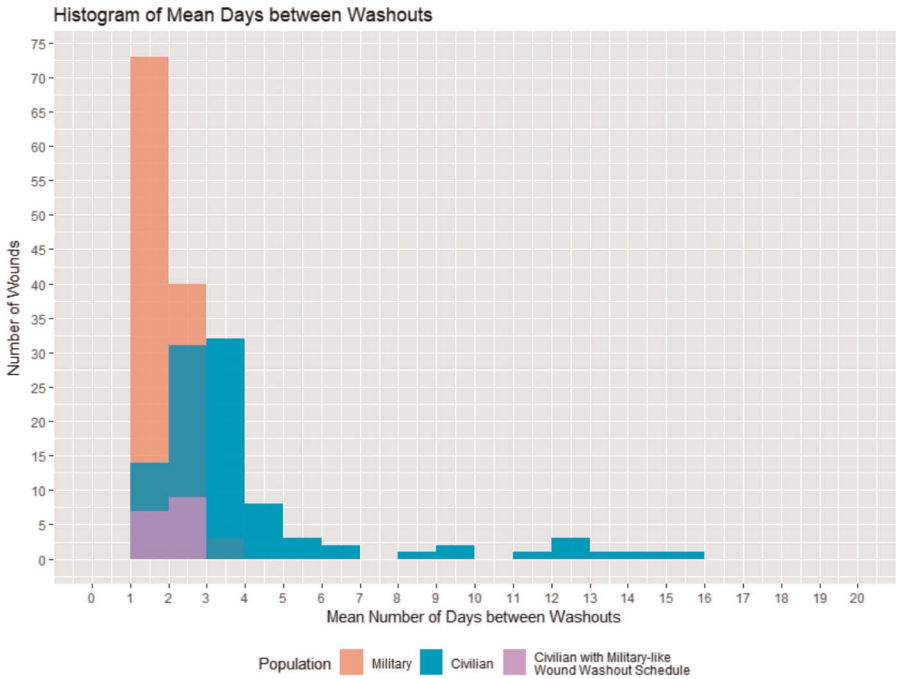

Figure 2. Histogram of mean days between washouts for the civilian population and military population. The Civilian MWS subset includes civilian wounds where the interval between wound washouts did not exceed 3 days at any point during wound care.

Grady Memorial Hospital in Atlanta, GA. Institutional approval from the respective institution's IRB was obtained prior to patient enrollment. Once patients were enrolled in this observational trial, their wounds were treated with the institution's standard of care and serum and wound effluent were collected at every operative washout and bedside negative pressure dressing change. At WRNMMC, strict wound management guidelines were followed which called for wound examination and washout approximately every 24 hours to 72 hours in the operating room and with patients remaining as inpatients until wounds were successfully closed.[1] This paradigm was followed as closely as possible although sometimes patients required longer intervals between washouts due to issues, such as patient stability and operating room availability. The CP treatment was much more variable, with operative washouts occurring less frequently, bedside dressing changes occurring more commonly, and outpatient wound management strategies occasionally pursued. All wounds underwent a coverage attempt of some sort, ranging from delayed primary closure or skin grafting to complex attempts at flap closure. Samples were collected using a previously published process and included serum and both tissue and wound effluent from each study wound.[4] We enrolled 73 MP and 83 CP with a total of 116 and 110 extremity wounds, respectively. Characteristics of patients and wounds, as well as outcomes, are listed in Table 1. Civilian wounds closed immediately after enrollment without a washout prior to wound closure were excluded from analysis. Using nonparametric two-sample Wilcoxon rank-sum tests, we compared the levels of 32 wound effluent biomarkers in these two populations at two points in their care: at first wound washout and at wound closure (for MP, "first wound washout" was the first washout upon admission to WRNMMC after transportation from overseas locations where patients were initially administered care after injury).

We then created a subset of the CP wounds where the wound care schedule approximately matched that of the MP population. We included in this subset those wounds in the CP where the interval between wound washouts did not exceed 72 hours at any point during wound care. We called this subset Civilians with Military-like Wound Washout Schedules (Civilian MWS). We repeated the two-sample Wilcoxon rank-sum tests for the biomarker levels at both first washout and wound closure, comparing the Civilian MWS to the MP population. We also produced 95% confidence intervals for the estimated differences in location parameters of effluent levels in the military population and the civilian population as well as in the military population and the Civilian MWS. Significance was set at p less than 0.05.

RESULTS

On average, the civilian population waited longer from the time of injury to closure (21.9 days, vs. 11.6 days, $p < 0.001$, Wilcoxon rank-sum test) (Fig. 1) and had a similar total number of washouts (3.86 vs. 3.44, $p = 0.52$, Wilcoxon rank-sum test). For wounds in the MP, the time between washouts for all wounds ranged from 1 days to 7 days, with a mean of 2.34 days and a median of 2 days. Average time between washouts per wound ranged from 1.5 days to 3.33 days. For wounds in the CP, the time between washouts for all wounds ranged from 1 day to 70 days, with a mean of 5.16 days and a median of 3 days. Average time between operative washouts per wound ranged from 1.5 days to 36.0 days. There were 16 wounds in the civilian population for which the number of days between washouts never exceeded 3 days. Figure 2 shows a histogram of the average days between washouts for the two populations.

Table 2 shows the results of performing two-sample Wilcoxon rank-sum tests on the levels of the 32 wound effluent

TABLE 2. *p* Values, Means, Estimates, and 95% Confidence Intervals From Two-Sample Wilcoxon Rank-Sum Comparing Civilian and Military Effluent Biomarker Levels

Effluent	*p* Value, Means, Estimate, and 95% CI at First Washout (Civ vs. Mil)	*p* Value, Means, Estimate, and 95% CI at First Washout (Civ-MWS vs. Mil)	*p* Value, Means, Estimate, and 95% CI at Wound Closure (Civ vs. Mil)	*p* Value, Means, Estimate, and 95% CI at Wound Closure (Civ-MWS vs. Mil)
EGF	0.137	0.479	0.134	0.483
	Mean Civ: 116.5 Mean Mil: 63.5 Estimate: −11.5 95% CI, −27.9 to 4.2	Mean Civ-MWS: 129.8 Mean Mil: 63.5 Estimate: 14.3 95% CI, −25.9 to 74.8	Mean Civ: 74.7 Mean Mil: 31.5 Estimate: −5.0 95% CI, −10.1 to 1.7	Mean Civ-MWS: 86.2 Mean Mil: 31.5 Estimate: 4.1 95% CI, −9.4 to 43.9
Eotaxin	$p < 0.001$	**$p < 0.001$**	**0.00197**	0.285
	Mean Civ: 46.8 Mean Mil: 137.8 Estimate: −60.1 95% CI, −87.1 to −40.1	Mean Civ-MWS: 29.6 Mean Mil: 137.8 Estimate: −62.9 95% CI, −120.6 to −28.2	Mean Civ: 85.8 Mean Mil: 157.8 Estimate: −36.6 95% CI, −68.9 to −11.8	Mean Civ-MWS: 80.6 Mean Mil: 157.8 Estimate: −28.0 95% CI, −97.7 to 25.2
FGF-Basic	0.0453	0.422	**$p < 0.001$**	**$p < 0.001$**
	Mean Civ: 68.1 Mean Mil: 60.0 Estimate: 13.0 95% CI, 0.2 to 27.5	Mean Civ-MWS: 63.8 Mean Mil: 60.0 Estimate: 12.2 95% CI, −19.7 to 38.5	Mean Civ: 57.1 Mean Mil: 23.6 Estimate: 31.6 95% CI, 24.8 to 38.6	Mean Civ-MWS: 59.5 Mean Mil: 23.6 Estimate: 30.5 95% CI, 16.3 to 48.0
G-CSF	$p < 0.001$	0.539	**0.0323**	0.630
	Mean Civ: 2713 Mean Mil: 862.9 Estimate: 789.8 95% CI, 284.2 to 1655	Mean Civ-MWS: 1303 Mean Mil: 862.9 Estimate: 79.2 95% CI, −292.4 to 1553	Mean Civ: 1728 Mean Mil: 1974 Estimate: −219.9 95% CI, −493 to −21.6	Mean Civ-MWS: 1511 Mean Mil: 1974 Estimate: −110.4 95% CI, −864.8 to 538.7
GM-CSF	0.285	0.174	**$p < 0.001$**	**0.0196**
	Mean Civ: 18.3 Mean Mil: 12.5 Estimate: −1.9 95% CI, −5.0 to 1.5	Mean Civ-MWS: 9.8 Mean Mil: 12.5 Estimate: −3.5 95% CI, −9.4 to 2.5	Mean Civ: 12.1 Mean Mil: 20.8 Estimate: −10.3 95% CI, −13.5 to −5.1	Mean Civ-MWS: 8.5 Mean Mil: 20.8 Estimate: −9.0 95% CI, −16.7 to −1.2
HGF	0.0711	0.959	**0.0102**	0.467
	Mean Civ: 4768 Mean Mil: 5053 Estimate: −862.7 95% CI, −1733 to 77.8	Mean Civ-MWS: 4934 Mean Mil: 5053 Estimate: −112.5 95% CI, −2603 to 2495	Mean Civ: 6892 Mean Mil: 7779 Estimate: −2168 95% CI, −3468 to −600.8	Mean Civ-MWS: 7247 Mean Mil: 7779 Estimate: −1201 95% CI, −3605 to 2440
IFN-α	$p < 0.001$	0.105	**0.00325**	0.0611
	Mean Civ: 84.0 Mean Mil: 75.7 Estimate: 25.6 95% CI, 11.5 to 45.7	Mean Civ-MWS: 69.8 Mean Mil: 75.7 Estimate: 17.6 95% CI, −5.1 to 41.3	Mean Civ: 88.5 Mean Mil: 75.7 Estimate: 19.5 95% CI, 6.3 to 34.8	Mean Civ-MWS: 84.3 Mean Mil: 75.7 Estimate: 23.8 95% CI, −1.5 to 45.9
IFN-γ	0.00223	0.680	0.712	0.878
	Mean Civ: 21.3 Mean Mil: 10.7 Estimate: 8.9 95% CI, 2.5 to 14.0	Mean Civ-MWS: 10.9 Mean Mil: 10.7 Estimate: 1.3 95% CI, −3.7 to 9.9	Mean Civ: 38.9 Mean Mil: 31.2 Estimate: 0.6 95% CI, −2.8 to 4.2	Mean Civ-MWS: 21.9 Mean Mil: 31.2 Estimate: 0.5 95% CI, −7.9 to 19.3
IL-10	0.00652	0.117	0.633	0.534
	Mean Civ: 66.4 Mean Mil: 97.8 Estimate: −20.6 95% CI, −38.4 to −5.7	Mean Civ-MWS: 50.6 Mean Mil: 97.8 Estimate: −22.7 95% CI, −66.7 to 7.1	Mean Civ: 58.2 Mean Mil: 69.9 Estimate: −2.2 95% CI, −11.0 to 6.1	Mean Civ-MWS: 37.1 Mean Mil: 69.9 Estimate: −5.0 95% CI, −31.7 to 10.9
IL-12	$p < 0.001$	**0.00125**	**$p < 0.001$**	**0.00314**
	Mean Civ: 104.4 Mean Mil: 142.4 Estimate: −44.9 95% CI, −66.7 to −21.9	Mean Civ-MWS: 72.3 Mean Mil: 142.4 Estimate: −65.9 95% CI, −102.3 to −32.6	Mean Civ: 110 Mean Mil: 205.2 Estimate: −88.3 95% CI, −112.9 to −63.2	Mean Civ-MWS: 109.7 Mean Mil: 205.2 Estimate: −84.3 95% CI, −128.9 to −34.0
IL-13	0.161	0.194	**0.0128**	0.318
	Mean Civ: 53.0 Mean Mil: 30.5 Estimate: 7.5 95% CI, −3.9 to 24.7	Mean Civ-MWS: 63.3 Mean Mil: 30.5 Estimate: 43.4 95% CI, −13.0 to 76.3	Mean Civ: 40.2 Mean Mil: 50.1 Estimate: −14.5 95% CI, −34.3 to −1.9	Mean Civ-MWS: 42.1 Mean Mil: 50.1 Estimate: −9.4 95% CI, −48.0 to 9.4

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TABLE 2. *(Continued)*

Effluent	*p* Value, Means, Estimate, and 95% CI at First Washout (Civ vs. Mil)	*p* Value, Means, Estimate, and 95% CI at First Washout (Civ-MWS vs. Mil)	*p* Value, Means, Estimate, and 95% CI at Wound Closure (Civ vs. Mil)	*p* Value, Means, Estimate, and 95% CI at Wound Closure (Civ-MWS vs. Mil)
IL-15	0.659	0.595	0.342	0.833
	Mean Civ: 373.3 Mean Mil: 262.9 Estimate: 12.3 95% CI, −49.0 to 80.1	Mean Civ-MWS: 426.5 Mean Mil: 262.9 Estimate: 68.4 95% CI, −107.1 to 303.2	Mean Civ: 318.6 Mean Mil: 196.1 Estimate: 21.5 95% CI, −24.5 to 66.3	Mean Civ-MWS: 284 Mean Mil: 196.1 Estimate: −12.1 95% CI, −122.4 to 61.6
IL-17	**0.0198**	0.966	***p* < 0.001**	0.101
	Mean Civ: 13.0 Mean Mil: 24.2 Estimate: −5.0 95% CI, −14.4 to −0.7	Mean Civ-MWS: 19.0 Mean Mil: 24.2 Estimate: −0.5 95% CI, −18.5 to 11.8	Mean Civ: 13.6 Mean Mil: 38.0 Estimate: −18.8 95% CI, −27.7 to −7.9	Mean Civ-MWS: 14.8 Mean Mil: 38.0 Estimate: −20.1 95% CI, −37.1 to 2.2
IL-1α	0.648	0.281	0.0816	**0.0168**
	Mean Civ: 859.5 Mean Mil: 424.1 Estimate: 37.9 95% CI, −74.2 to 320.8	Mean Civ-MWS: 560 Mean Mil: 424.1 Estimate: −78.5 95% CI, −289.3 to 184.8	Mean Civ: 861.1 Mean Mil: 682.4 Estimate: −90.3 95% CI, −208.2 to 10.0	Mean Civ-MWS: 346.6 Mean Mil: 682.4 Estimate: −203.8 95% CI, −598.9 to −30.3
IL-1β	***p* < 0.001**	**0.0425**	0.756	0.386
	Mean Civ: 1427 Mean Mil: 110.4 Estimate: 466.1 95% CI, 128.6 to 615.8	Mean Civ-MWS: 374.7 Mean Mil: 110.4 Estimate: 34.4 95% CI, 1.1 to 120.5	Mean Civ: 1113 Mean Mil: 1176 Estimate: −12 95% CI, −111.6 to 104.1	Mean Civ-MWS: 407.4 Mean Mil: 1176 Estimate: −63.4 95% CI, −571.9 to 90.1
IL-2	0.589	0.173	0.397	0.505
	Mean Civ: 11.5 Mean Mil: 5.8 Estimate: 0.6 95% CI, −1.1 to 2.5	Mean Civ-MWS: 24.4 Mean Mil: 5.8 Estimate: 4.0 95% CI, −2.0 to 39.4	Mean Civ: 9.9 Mean Mil: 8.9 Estimate: −0.5 95% CI, −1.6 to 0.9	Mean Civ-MWS: 11.9 Mean Mil: 8.9 Estimate: −0.9 95% CI, −3.5 to 3.7
IL-2R	0.212	0.489	0.321	0.248
	Mean Civ: 567.6 Mean Mil: 513.2 Estimate: 73.7 95% CI, −46.9 to 209.9	Mean Civ-MWS: 416.8 Mean Mil: 513.2 Estimate: −65.5 95% CI, −268 to 127.5	Mean Civ: 958.2 Mean Mil: 775 Estimate: −71.4 95% CI, −211.1 to 77.8	Mean Civ-MWS: 584.5 Mean Mil: 775 Estimate: −145.4 95% CI, −401 to 90.0
IL-3	$p < 0.001$	***p* < 0.001**	***p* < 0.001**	**0.0152**
	Mean Civ: 77.2 Mean Mil: 8.6 Estimate: 27.6 95% CI, 16.3–57.8	Mean Civ-MWS: 168.5 Mean Mil: 8.6 Estimate: 30.7 95% CI, 21.7–103.5	Mean Civ: 46.3 Mean Mil: 9.3 Estimate: 14.2 95% CI, 7.3–22.4	Mean Civ-MWS: 89.8 Mean Mil: 9.3 Estimate: 13.7 95% CI, 4.2–108.1
IL-4	$p < 0.001$	**0.00246**	0.102	0.534
	Mean Civ: 37.3 Mean Mil: 13.1 Estimate: 13.2 95% CI, 4.1–28.1	Mean Civ-MWS: 54.1 Mean Mil: 13.1 Estimate: 37.5 95% CI, 22.2–72.5	Mean Civ: 28.8 Mean Mil: 18.4 Estimate: 4.6 95% CI, −0.8 to 12.1	Mean Civ-MWS: 30.6 Mean Mil: 18.4 Estimate: 5.6 95% CI, −7.3 to 28
IL-5	$p < 0.001$	***p* < 0.001**	0.176	0.505
	Mean Civ: 28.0 Mean Mil: 14.6 Estimate: 10.2 95% CI, 4.9–14.9	Mean Civ-MWS: 30.2 Mean Mil: 14.6 Estimate: 15.5 95% CI, 9.0–35.8	Mean Civ: 39.1 Mean Mil: 55.7 Estimate: −5.3 95% CI, −13.6 to 2.5	Mean Civ-MWS: 35.5 Mean Mil: 55.7 Estimate: −4.9 95% CI, −29.3 to 12.8
IL-6	0.496	0.853	***p* < 0.001**	0.837
	Mean Civ: 7.2e+04 Mean Mil: 1.1e+06 Estimate: −3231 95% CI, −1.5e+04 to 3.7e+04	Mean Civ-MWS: 5.9e+04 Mean Mil: 1.1e+06 Estimate: 7162 95% CI, −2.3e+04 to 5.2e+04	Mean Civ: 5.5e+04 Mean Mil: 2.3e+06 Estimate: −1.1e+04 95% CI, −1.7e+04 to −6996	Mean Civ-MWS: 4.4e+04 Mean Mil: 2.3e+06 Estimate: 3812 95% CI, −3.1e+04 to 4.0e+04
IL-7	0.0318	0.0736	**0.00399**	0.0639
	Mean Civ: 98.8 Mean Mil: 73.8 Estimate: 28.2 95% CI, 1.9–57.7	Mean Civ-MWS: 113.4 Mean Mil: 73.8 Estimate: 66.1 95% CI, −11.5 to 96.0	Mean Civ: 79.5 Mean Mil: 115.9 Estimate: −28.8 95% CI, −47.9 to −9.8	Mean Civ-MWS: 66.9 Mean Mil: 115.9 Estimate: −42.3 95% CI, −87 to1, 2.0

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TABLE 2. *(Continued)*

Effluent	*p* Value, Means, Estimate, and 95% CI at First Washout (Civ vs. Mil)	*p* Value, Means, Estimate, and 95% CI at First Washout (Civ-MWS vs. Mil)	*p* Value, Means, Estimate, and 95% CI at Wound Closure (Civ vs. Mil)	*p* Value, Means, Estimate, and 95% CI at Wound Closure (Civ-MWS vs. Mil)
IL-8	**$p < 0.001$**	**0.0273**	**$p < 0.001$**	**0.0330**
	Mean Civ: 5.5e+04 Mean Mil: 2.3e+04 Estimate: 2.3e+04 95% CI, 1.7e+04 to 3.1e+04	Mean Civ-MWS: 3.6e+04 Mean Mil: 2.3e+04 Estimate: 1.3e+04 95% CI, 1481 to 2.2e+04	Mean Civ: 3.0e+05 Mean Mil: 3.0e+04 Estimate: 2.4e+04 95% CI, 1.7e+04 to 3.4e+04	Mean Civ-MWS: 4.7e+04 Mean Mil: 3.0e+04 Estimate: 1.4e+04 95% CI, 1822 to 2.3e+04
IL-1RA	**$p < 0.001$**	0.0609	**0.00185**	**0.00887**
	Mean Civ: 9797 Mean Mil: 4285 Estimate: 2095 95% CI, 995.7–3220	Mean Civ-MWS: 5084 Mean Mil: 4285 Estimate: 1524 95% CI, −110.5 to 2761	Mean Civ: 1.5e+04 Mean Mil: 2.3e+04 Estimate: −8247 95% CI, −1.4e+04 to −2948	Mean Civ-MWS: 9375 Mean Mil: 2.3e+04 Estimate: −1.4e+04 95% CI, −2.2e+04 to −2954
IP-10	**$p < 0.001$**	**$p < 0.001$**	**$p < 0.001$**	**$p < 0.001$**
	Mean Civ: 69.2 Mean Mil: 7288 Estimate: −468.8 95% CI, −824, −286	Mean Civ-MWS: 50.7 Mean Mil: 7288 Estimate: −475.1 95% CI, −2560 to −191.3	Mean Civ: 290.1 Mean Mil: 4932 Estimate: −208 95% CI, −382.3 to −132.4	Mean Civ-MWS: 252.2 Mean Mil: 4932 Estimate: −261.7 95% CI, −661.7 to −113.7
MCP-1	0.0623	0.304	0.630	**0.0183**
	Mean Civ: 1.7e+04 Mean Mil: 4.9e+04 Estimate: 4162 95% CI, −194.8 to 8139	Mean Civ-MWS: 2.6e+04 Mean Mil: 4.9e+04 Estimate: 3569 95% CI, −4811 to 8559	Mean Civ: 1.9e+04 Mean Mil: 1.3e+05 Estimate: −1121 95% CI, −4918 to 3177	Mean Civ-MWS: 2.7e+04 Mean Mil: 1.3e+05 Estimate: 1.1e+04 95% CI, 777.3 to 2.1e+04
MIG	0.628	0.359	0.136	0.703
	Mean Civ: 54.1 Mean Mil: 154.8 Estimate: 2.7 95% CI, −8.8 to 16.1	Mean Civ-MWS: 30.9 Mean Mil: 154.8 Estimate: −8.2 95% CI, −48.9 to 9.1	Mean Civ: 136.5 Mean Mil: 243.6 Estimate: 16.2 95% CI, −5.2 to 39.8	Mean Civ-MWS: 114.8 Mean Mil: 243.6 Estimate: −7.9 95% CI, −38.2 to 43.7
MIP-1α	**$p < 0.001$**	0.992	**0.0114**	0.556
	Mean Civ: 3192 Mean Mil: 424.9 Estimate: 430.5 95% CI, 159–967	Mean Civ-MWS: 1824 Mean Mil: 424.9 Estimate: 2.1 95% CI, −119.4 to 245.4	Mean Civ: 3327 Mean Mil: 4.7e+04 Estimate: −470.3 95% CI, −1099 to −137.9	Mean Civ-MWS: 3791 Mean Mil: 4.7e+04 Estimate: −247.6 95% CI, −2653 to 1067
MIP-1β	**0.00396**	0.103	**$p < 0.001$**	0.178
	Mean Civ: 2498 Mean Mil: 953.1 Estimate: 282.5 95% CI, 87.7–607.1	Mean Civ-MWS: 1860 Mean Mil: 953.1 Estimate: 263.9 95% CI, −63.9 to 1155	Mean Civ: 3853 Mean Mil: 5.2e+04 Estimate: −1387 95% CI, −2261 to −680	Mean Civ-MWS: 3461 Mean Mil: 5.2e+04 Estimate: −955.7 95% CI, −5132 to 404.3
RANTES	**$p < 0.001$**	**$p < 0.001$**	**$p < 0.001$**	0.737
	Mean Civ: 310.2 Mean Mil: 3550 Estimate: −1902 95% CI, −2368 to −1593	Mean Civ-MWS: 144.1 Mean Mil: 3550 Estimate: −1993 95% CI, −2928 to −1476	Mean Civ: 231.1 Mean Mil: 844.6 Estimate: −179 95% CI, −320.5 to −93.8	Mean Civ-MWS: 598.2 Mean Mil: 844.6 Estimate: −32.8 95% CI, −307.1 to 277.5
TNF-α	**$p < 0.001$**	0.556	0.554	0.192
	Mean Civ: 385.6 Mean Mil: 69.7 Estimate: 89.1 95% CI, 28.8 to 169.1	Mean Civ-MWS: 252.9 Mean Mil: 69.7 Estimate: 6.7 95% CI, −12.6 to 324.4	Mean Civ: 499 Mean Mil: 529.3 Estimate: −6.0 95% CI, −36.4 to 23.6	Mean Civ-MWS: 306.3 Mean Mil: 529.3 Estimate: −23.8 95% CI, −212.7 to 14.7
VEGF	$p < 0.001$	0.0192	0.124	0.932
	Mean Civ: 183.7 Mean Mil: 56.1 Estimate: 71.0 95% CI, 36.5–106.3	Mean Civ-MWS: 83.8 Mean Mil: 56.1 Estimate: 27.5 95% CI, 4.8–56.3	Mean Civ: 230.4 Mean Mil: 150.6 Estimate: 27.8 95% CI, −7.1 to 67.3	Mean Civ-MWS: 169.3 Mean Mil: 150.6 Estimate: 4.5 95% CI, −53.7 to 88.7

p Values in bold emphasis indicate statistically significant differences at a significance level of 0.05.
Estimates are of the difference in location parameters between the civilian population (or subset) and the military population (this is not equivalent to the difference in means).
Civ, civilian; Mil, military; 95% CI, 95% confidence interval.

biomarkers. The second and fourth columns show the *p* values, means, estimates, and 95% confidence intervals resulting from performing the test comparing the entire civilian population to the military population at first washout and wound closure. The third and fifth columns show the *p* values, means, estimates, and 95% confidence intervals resulting from comparing the Civilian MWS

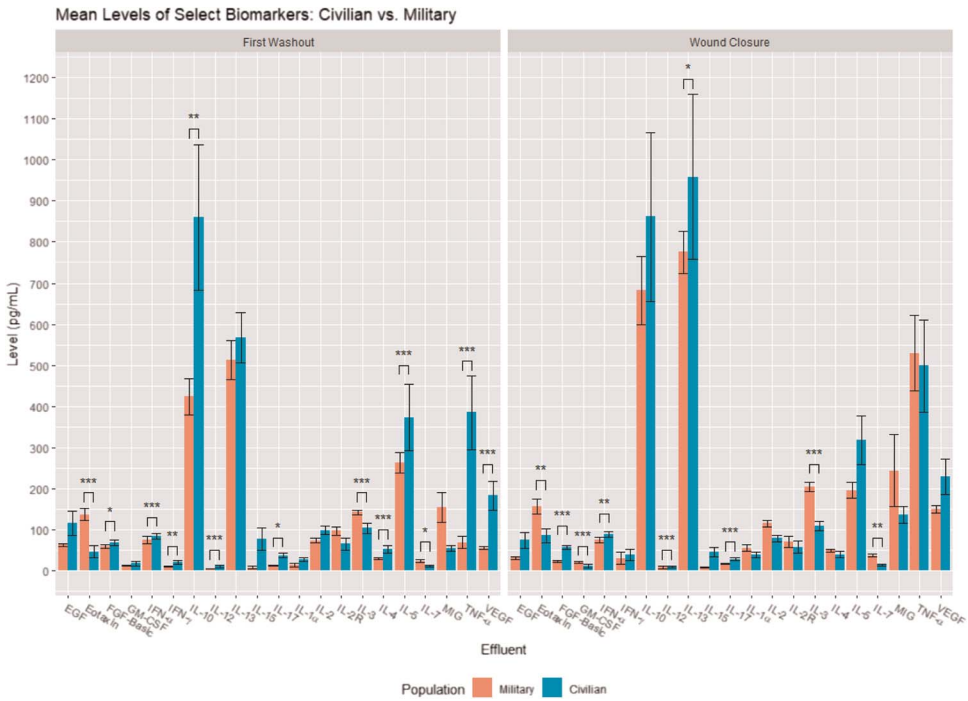

Figure 3. Mean levels of select biomarkers at first washout and wound closure for the civilian population and military population. biomarker levels were measured in pg/mL. G-CSF, HGF, IL-1β, IL-6, IL-8, IL-1RA, IP-10, MCP-1, MIP-1α, MIP-1β, and RANTES were not included due to constraints in the scale of the graph. Error bars show the standard error of the mean. Statistically significant differences are marked with asterisks (*0.05, **0.01, ***0.001).

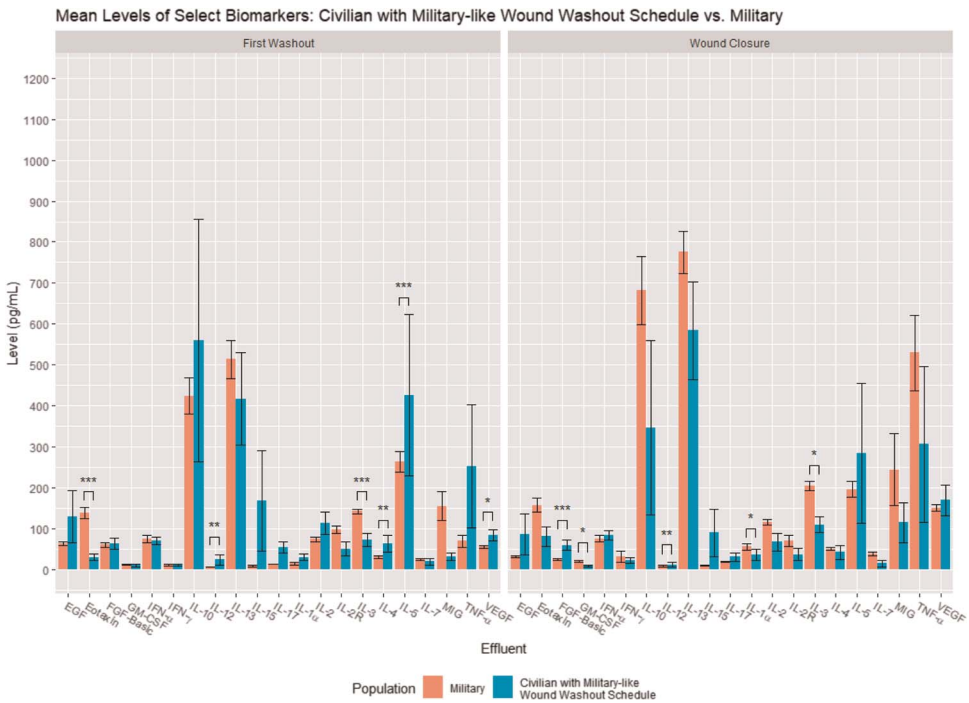

Figure 4. Mean levels of select biomarkers at first washout and wound closure for the Civilian MWS and military population. Biomarker levels were measured in pg/mL. G-CSF, HGF, IL-1β, IL-6, IL-8, IL-1RA, IP-10, MCP-1, MIP-1α, MIP-1β, and RANTES were not included due to constraints in the scale of the graph. Error bars show the standard error of the mean. Statistically significant differences are marked with asterisks (*0.05, **0.01, ***0.001).

subset to the MP at first washout and wound closure. Estimates and 95% confidence intervals are for the difference in location parameters between the civilian population or Civilian MWS subset and the military population. The difference in location parameters is defined as the median of the difference between a sample from the first population and a sample from the second and does not correspond to the difference in means of the two populations.

As the table shows, when the wound effluent biomarker levels measured on the MP are compared with the entire civilian population at wound closure, we see 18 (56.3%) biomarkers with p values indicating a significant ($p < 0.05$) difference. Conversely, when we restrict our analysis to the Civilian MWS subset, we find far fewer significant ($p < 0.05$) differences in levels of biomarker. Indeed, only 9 (28.1%) biomarkers (FGF-basic, GM-CSF, IL-12, IL-1α, IL-3, IL-8, IL-1RA, IP-10, and MCP-1) continue to show significant ($p < 0.05$) differences using the Civilian MWS subset. Of these, FGF-basic, IL-3, and IL-8 had a higher mean effluent biomarker level in the Civilian MWS than in the military population. Of the biomarkers that showed significant differences in effluent levels between the civilian population and military population both at first washout and at wound closure, the direction of the difference remained the same except for G-CSF, IL-7, IL-1RA, MIP-1α, and MIP-1β, where the mean effluent level was higher in the civilian population at first washout, but higher in the military population at wound closure.

For select biomarkers, Figures 3 and 4 show how the differences in mean effluent levels for the military and civilian populations converge as the civilian population is restricted to wounds with washout schedules that are similar to the military washout schedule. Standard errors of the mean effluent biomarker levels were in general increased in the Civilian MWS compared with the entire civilian population.

DISCUSSION

Clinical decision support tools are becoming ubiquitous in the clinical arena.[3] The proliferation of smart phones and electronic medical records have allowed these tools to be more robust and more complex and to further society's desire for individualized, precise clinical care. Most, however, have been based on clinical or administrative data, limiting their capacity to impute unique biologic signatures. Accordingly, wound management strategies in civilian centers remain surgeon- and service-specific, and in many cases, the decision for timing of closure is based heavily on clinical gestalt. Furthermore, in a busy urban civilian trauma center, surgeons have limitations on certain resources including operating room availability and the ability to maintain patients as inpatients for prolonged periods of time. Therefore, there is great variability in wound management prior to a coverage attempt. This severely hampers the ability of a biologically based CDST to accurately predict wound closure success, as the biology of the wounds seem to be very different based on their recent management strategy. In fact, several wounds in the civilian population were treated with outpatient negative pressure dressings for weeks between the last inpatient therapy and the attempt at closure. While this unfortunately limits the applicability of the biomarker profile of the preclosure washout in terms of predictive capacity, it is a reality in many civilian centers in an effort to conserve operative resources and hospital lengths of stay.

Civilian trauma centers also see a more variable patient population in terms of age, sex, and general overall health. As Surgical Critical Care Initiative has worked to adapt WounDx for use in a civilian setting, one of the obstacles has been understanding the causes of the differences in effluent biomarker levels between the military population (from which WounDx was developed) and the civilian population. Broadly, the possible causes are either the differences in baseline physiology, differences in wound care, or the differences caused by the mechanism of wounding (i.e., blast injury vs. nonblast injury). If the primary cause for differences in the measured wound effluent inflammatory biomarker levels arises from physiological differences between the two populations, then the data collected from the military population cannot be used in developing a CDST for wound closure for the civilian population. The results presented here, however, suggest that the differences arise in part from heterogeneity in wound management, specifically the aggressiveness and timing of operative washouts.

In this study, the use of WounDx™ has allowed us to assess the relative impact of biology and administrative process on wound outcome. The nine biomarkers that continue to show significant differences between the military population and civilian population with military-like wound washout schedule at wound closure (FGF-basic, GM-CSF, IL-12, IL-1α, IL-3, IL-8, IL-1RA, IP-10, and MCP-1) all have important roles in immune system signaling. Of those, IL-8, IP-10, and MCP-1 are chemokines that induce chemotaxis in nearby cells and recruit leukocytes to sites of inflammation. It can be speculated that the different levels of these biomarkers are a result of a different biologic response in the MPs, who, compared with the civilian patients, are younger and generally more fit.[6,7]

Alternatively, the MPs experienced a greater proportion of blast injuries and amputations compared with the civilian patients, and there has been research showing that osteoclast levels increase after bone injury.[8] GM-CSF, IL-1α, IP-10, and MCP-1 are associated with osteoclast activity and formation and are elevated in the MPs compared with the Civilian MWS subset at wound closure.[9–14] A greater proportion of substantial bone injuries and fractures could explain the elevated levels of GM-CSF, IL-1α, and IP-10 in the Military population compared with in the Civilian MWS subset, where injuries primarily arose from gunshot wounds or crush injuries. FGF-basic and IL-3 have been shown to be involved in osteogenesis[15,16] and had higher mean effluent levels in the Civilian MWS subset. Increased osteoclast activity over time after serious bone injuries in the MPs could also explain why levels of MIP-1α and MIP-1β are elevated in the civilian patients compared to the MPs at first washout but are elevated in the MPs compared with the civilian patients at wound closure.[17,18]

Future work is required to better understand the differences in wound biomarker levels between the two populations and why they arise. Establishing causation between wound care regimens and wound closure outcomes requires larger data sets and a more rigorous analysis with a clinical trial. Moreover, in this analysis, there were only 16 wounds in the Civilian MWS subset, resulting in large standard errors of the mean effluent cytokine levels in the subset. A study with a larger population of civilian patients with military-like washout schedules would advance our understanding of the sources of the differences in wound effluent cytokine levels between the two populations and

would increase the power of the Wilcoxon rank-sum tests to detect differences in cytokine levels between the populations, particularly differences with small effect sizes. The Surgical Critical Care Initiative collaborative continues to conduct these studies.

One more limitation of our research is that the statistical analysis performed here falls short of showing that the levels of all wound effluent biomarkers are statistically the same for the military and civilian populations if the civilian population were cared for following the military protocol. Further analysis of this data may allow for stronger conclusions to be drawn regarding the sources of variability in wound biomarker levels between the two populations. Individual biomarkers could be assessed for their role in wound healing or for correlations with wound healing outcome.

In medical care today, precision medicine is a growing field, where treatment and care are tailored to individuals for better likelihood of success. By predicting injury outcomes in patients, prevention strategies can be taken to reduce the chances of adverse outcomes and complications, such as wound dehiscence, which can lead to infections and delayed wound healing. A CDST is one way of applying medicine to patient care, by providing patient-specific information to assist clinicians in reaching decisions about treatment options. The intention of a CDST is not to replace clinician judgment, but rather to guide and inform a decision making process. A tool, such as WounDx, has been shown to be useful both in preventing failed wound closure attempts and their associated morbidity while also avoiding unnecessary washouts in wounds that are biologically ready to close, allowing for the conservation of resources.[3] Therefore, it is felt that standardizing traumatic wound treatment, augmented as possible with CDSTs, so that it is not solely based on subjective criteria, such as wound appearance, will contribute to increased consistency and quality of patient care. An association of washout frequency with wound biological factors suggests that washouts may contribute to the healing process[19,20] and that similar washout frequencies leads to convergence of wound biology, even in patients who do not share demographic characteristics. Techniques and tools that enable reliable predictions of wound closure will lead to a greater ability to predict resource needs and costs associated with the treatment of extremity wounds. Development of a CDST that can be used both for military and civilian populations to predict wound outcome will be crucial in advancing the current state of traumatic wound care.

AUTHORSHIP

C.J.D. participated in the study design, data collection and interpretation, writing, critical revision. E.S. participated in the study design, data analysis and interpretation, writing, critical revision. A.S. participated in the study design, data analysis and interpretation, writing, critical revision. S.S. participated in the study design, data analysis and interpretation, critical revision. V.K. participated in the data analysis and interpretation, writing, critical revision. B.K.P. participated in the study design, data interpretation, critical revision. J.A.F. participated in the study design, data interpretation, critical revision. T.B. participated in the study design, data interpretation, critical revision. A.D.K. participated in the study design, data interpretation, critical revision. E.E. participated in the study design, data interpretation, critical revision.

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DISCLOSURE

The authors declare no conflicts of interest.

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