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Early clinical complete blood count changes in severe burn injuries

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ABSTRACT

Introduction: Following a severe burn injury, significant hematologic changes occur that are reflected in complete blood count (CBC) measurements. Our aim for this study was to examine trend in the components of the CBC in severely burned patients over the first week after injury and compare differences in CBC components between survivors and non-survivors.
Methods: A 5-year retrospective review was performed of adult (≥18 years) burn patients with a TBSA ≥ 15%. Age, TBSA, gender, mortality, length of hospital stay, ventilator days, and CBC were collected.
Results: Over the first week after injury, HBG and HCT decreased. This decrease was due to loss of red blood cells. WBC counts was initially elevated but decreased over the first 4 days. PLT also decreased over the first 4 days. Non-survivors had lower HBG, HCT, RCC, and PLT over the first week compared to survivors. Non-survivors had higher WBC compared to survivors. RDW was elevated during the first week in non-survivors. MPV was elevated at the end of the first week in non-survivors and MPV on day 7 was independently associated with mortality (O.R. 2.01 (1.1–3.7)). Compared to survivors non-survivors received more transfusions of blood products during the first week after injury.
Conclusion: Burn-injury specific trends in CBC measurements can be used as references to determine expected clinical course of burn patients. Non-survivors have early hematologic differences compared to survivors.

1. Introduction

It has been well established that following a severe burn injury, there is a progressive anemia caused by dilution from resuscitation, blood loss from open wounds, and hemolysis [1]. Additionally, other cells in the plasma such as white blood cells (WBC) and platelets (PLT) can either be abnormally high or low following a severe burn injury as a result of systemic inflammation [2,3]. These changes are well known and impact resource utilization, such as blood product transfusion, and impact clinical and surgical decision-making [4].

Current clinical evaluation of complete blood count (CBC) assays relies on reference values from normal or non-diseased individuals. Establishing an expected trend for CBC indices in

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the immediate few days following a severe burn injury may provide clinicians with a burn-injury specific reference for CBC assays. This will allow clinicians to determine if a component of the CBC is outside the expected reference range for severely burned patients. Additionally, if CBC indices are trended for survivors and non-survivors, references can be established that may help clinicians determine the clinical trajectory of a burn patient. Early changes in red blood cells morphology may be important clinical markers of pathology [5]. For example, changes in red cell distribution width may be a risk factor death in severely ill patients [6]. Additionally, changes in platelet size may also indicate a higher risk of death in critically ill patients [7]. Our goal for this investigation was to trend CBC assay components during the first week after a severe burn injury and compare differences between survivors and non-survivors. We hypothesized that there would be burn-injury early specific changes in several components of a CBC assays that are outside of established reference ranges and that there would also be early differences in several components of a CBC assay between survivors and non-survivors.

2. Methods

We performed a retrospective review from 2010 to 2015 of acute burn-injured adult (≥18 years) patients admitted to our regional burn center. We received regulatory approval for our investigation from the local institutional review board. We included patients who were at least 18 years old and had a burn injury of ≥15% TBSA (% total body surface area of burn). We excluded patients were deemed to have a non-survivable burn injury by the admitting burn surgeon. We collected data on age, burn injury, length of hospital stay, ventilator days, and complete blood count (CBC) over the first week after injury. All patients included in the study had at least one CBC performed per day for the first 7 days after injury. We collected the first admission CBC and then the first CBC that was reported each day. The CBCs were performed in the hospital's CLIA (Central Laboratory Improvement Amendment) approved laboratory. All of the CBC assays were automated CBC assays on a Beckman-Coulter CBC analyzer. White blood cell counts (WBC) and platelet counts (PLT) are reported as 1000 cells/cubic millimeter (k/mm^3), (RCC) red cell count is reported in 1 million cells/cubic millimeter (m/mm^3), hemoglobin (HGB) is reported in grams/deciliter (gm/dl), hematocrit (HCT) is reported in percentage (%), mean corpuscular volume (MCV) and mean platelet volume (MPV) is reported in cubic micrometer (um^3), mean corpuscular hemoglobin (MCH) is reported in picograms (pg), mean corpuscular hemoglobin concentration (MCHC) is reported in percentage (%), and red blood cell distribution (RDW) width is reported in percentage (%).

Statistical analysis was performed using R-statistical software (www.r-project.org). All data variables were tested for normality using the Wilk–Shapiro test. Comparisons of means of continuously collected non-normally distributed data were tested using the Wilcox-rank-sum test. Comparisons of means of continuous collected normally distributed data were tested using the student's t-test. The Fisher exact test was use to determine differences between groups for categorical data. We created a multivariate model of the data collected to determine if any hematologic variable collected was independently associated with mortality. We analyzed the models using multivariate logistic regression. We used a stepwise subtraction technique and determined the best fit model by the Akiake Information Criterion. All significance values were set at a p-value <0.05. All mean values are represented by mean±standard deviation and all median values are represented by median (interquartile range (25%–75%)).

3. Results

A total of 191 patients were included in the investigation. The majority of the patients were men (88%). Mean age was 45 ±17 years and mean TBSA was 32±18% and 12% of the patients died (Table 1). Non-survivors were significantly older (58±14 years) compared to survivors (43±17 years). Non-survivors also had significantly larger TBSA (47±23% vs. 30 ±17%) and longer median ventilator days (26 (13–36) days vs. 2 (0–11) days) compared to survivors. There was no difference in median length of hospital days (26(16–36) days vs. 24 (17–44) days) (Table 2).

For all patients, mean white blood cell count (WBC) dropped each day significantly from admission (19±8 k/mm^3) to a nadir at days 3 (5±3 k/mm^3) and 4 (5±3 k/mm^3) after injury. Starting on day 5, WBC increased and reached a mean of 10±5 k/mm^3 one week after injury. Mean HGB was 15±2 gm/dl on admission and decreased everyday. At one week after injury, mean HGB was 9±2 gm/dl. As expected, HCT also followed a similar pattern as HGB. RCC followed a similar pattern as hemoglobin decreasing from 4.9±0.8 m/mm^3 on admission to 3±0.5 m/mm^3 by day 6 and 7. MCV and MCHC both remained similar from admission to day 7. This confirms that the decrease in hemoglobin from admission was from a loss of circulating red blood cells. RDW increased from 14±1.3% on admission to 15 ±1.7% by day 7. PLT started at 230±89 k/mm^3 on admission and dropped to a low of 123±51 on day 4. By day 7, PLT rebounded to a mean of 202±81. However, MPV did not change significantly from admission (Fig. 1).

There were no significant differences in mean WBC between survivors and non-survivors except on days 3 and 4 on which non-survivors had a higher mean WBC. On day 3 survivors had a mean WBC of 4.8±2.8 k/mm^3 and non-survivors had a mean WBC of 6.1±5 k/mm^3 (p=0.01). On day

Table 1 – Demographic of patients included in the analysis. (TBSA—total body surface area burned), LOS—length of hospital stay), VENT—ventilator days).

Variable	Value
Subjects	191
Age (years)	45±25
Men	148
Women	42
TBSA (%)	32±18
LOS (days)	24 (17–43)
VENT (days)	2 (0–19)
Died (%)	12%

Table 2 – Comparison of survivors and non-survivors. (TBSA—total body surface area burned), LOS—length of hospital stay), VENT—ventilator days).

Variable	Lived	Died	p-Value
Age (years)	43±17	58±18	0.0004
Men	131	18	
Women	37	5	1.0
TBSA (%)	30±17	47±23	0.003
LOS (days)	24 (17–44)	26 (16-36)	0.59
VENT (days)	2 (0-11)	26 (13-36)	0.000001
PRBC transfused first week	1 (0-5)	5 (2.5-12)	0.0001
FFP transfused first week	0 (0-2)	2 (0.5-6)	0.0003
PLT transfused first week	0 (0)	1 (0-2)	0.00009

4 survivors had a mean WBC of 4.8±2.5k/mm^3 and non-survivors had a mean WBC of 6.4±4k/mm^3 (p=0.04). WBC increased on the subsequent days for both survivors and non-survivors and by day 7 was a mean of 9.5±4.6k/mm^3 for survivors and 10.7±4.7k/mm^3 for non-survivors. Mean HGB and HCT were significantly lower from admission in non-survivors compared to survivors. On admission mean HGB and HCT were 14±3mg/dl and 40±8% for non-survivors, while admission mean HGB and HCT were 15 ±2gm/dl and 48±7% for survivors (p=0.03, p=0.02 respectively). By day 7, mean HGB and HCT were 8.4±1.3gm/dl and 25±4% for non-survivors, while day 7 mean HGB and HCT were 9.4±1.7gm/dl and 28±5% for survivors (p=0.01, p=0.01 respectively). Red cell count was also significantly lower from admission in non-survivors. Non-survivors had a mean RCC on admission of 4±0.9m/mm^3 and survivors had a mean RCC of 5±0.8m/mm^3 (p=0.005). Everyday, RCC decreased in both groups but was significantly lower each day in the non-survivors. By day 7, non-survivors had a mean RCC of 2.7±0.4m/mm^3 and survivors had a mean RCC of 3.1±0.5m/mm^3 (p=0.004). There were no differences in MCV or MCHC between survivors and non-survivors. RDW was significantly higher from admission and everyday for 7 days following the burn injury in non-survivors, indicating that non-survivors had more circulating immature red blood cells (RBC) or had more RBC with altered morphology. On admission, non-survivors had a mean RDW of 14.7±2% and survivors had a

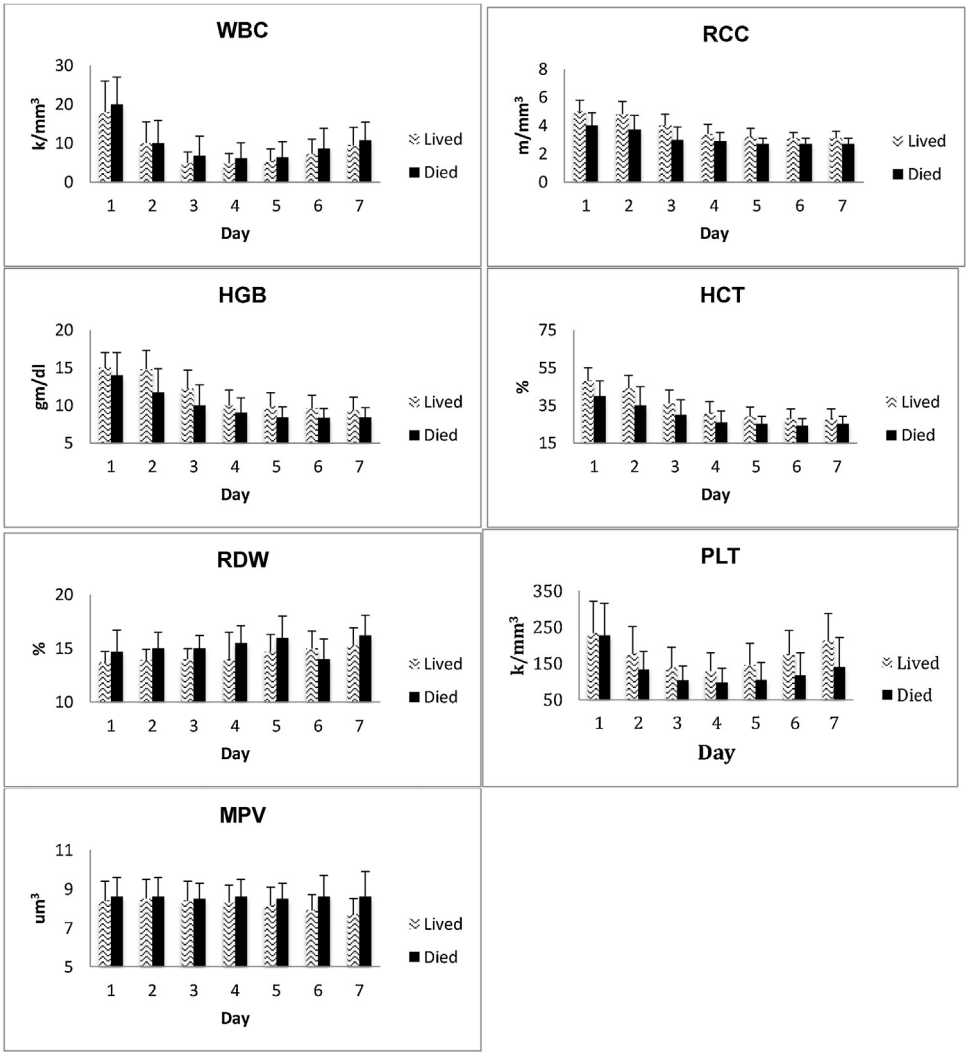

Fig. 1 – Hematologic changes over the first 7 days after burn injury in survivors and non-survivors. (WBC—white blood cell count (k/mm^2), HBG—hemoglobin (gm/dl), HCT—hematocrit (%), PLT—platelets (k/mm^2), RDW—red cell distribution width (%), MPV—mean platelet volume (um^3)).

mean RBW of 13.7±1% (p=0.0006). By day 7, non-survivors had an RDW of 16.2±1.9%, while non-survivors had a mean RDW of 15.3±1.6%. On admission, there was no difference in PLT between survivors and non-survivors. However, by day 2, there was a significant difference in PLT. Survivors had a significantly higher PLT (178±73k/mm^3) compared to non-survivors (132±51k/mm^3, p=0.007). This trend continued through day 7 when mean PLT was 213±75k/mm^3 for survivors and 140±81k/mm^3 for non-survivors (p=0.0001). MPV remained similar for both survivors and non-survivors from admission to day 5. On day 6 and 7, MPV was significantly higher in non-survivors compared to survivors indicating that there may have been more immature platelets in circulation for non-survivors on at the end of the first week after injury. On day 6, MPV was 8.6±1.1um^3 for non-survivors and 7.9±0.8um^3 for survivors (p=0.01). On day 7, MPV was 8.6±1.3um^3 for non-survivors and 7.7±0.8um^3 for survivors (p=0.00001).

Over the first week of admission after burn injury, a total of 842 units of packed red blood cells (PRBC), 333 units of fresh frozen plasma (FFP), and 109 units of platelets (PLT) were transfused. Non-survivors received more PRBC units than survivors (5 (2.5–12) units vs. 1 (0–5) units, p=0.0001). Non-survivors also were transfused more units of FFP (2 (0.5–6) units vs. 0 (0–2) units, p=0.003) and PLT (1 (0–2) units vs. 0 units, p=0.00009) (Table 2).

We created a multivaritate linear regression model to determine if either RDW or MPV were associated with increased length of hospital stay or increased ventilator days. Neither RDW nor MPV were independently associated with either outcome. Only age and TBSA were independently associated with increased ventilator days and only TBSA was independently associated with increased length of hospital stay. We also created a multivariate logistic regression model to determine any independent variables for mortality. Our best-fit model included the following variables: TBSA, age, and MPV on day 7. All three variables were independently associated with an increased risk of death. The odds ratio for TBSA was 1.07 (1.04–1.11), the odds ration for age was 1.09 (1.05–1.14), and the odds ratio of MPV on day 7 was 2.01 (1.1–3.7). MPV on day 7 was the only hematologic variable that was independently associated with death.

4. Discussion

Our results show that for severely burned patients, there are early burn-injury specific trends for components of the CBC assay. As expected, hemoglobin and hematocrit decreased over the first week after injury. This is likely due to a loss of red blood cells and not from a loss of hemoglobin since red cell count also decreased from admission to 1 week after injury but mean corpuscular hemoglobin concentration did not change. The loss of red blood cells in the first few days following a severe burn is likely due to hemolysis of red blood cells [2]. Following this early period, alterations in the bone marrow production of erythroid lineages probably results in the persistence of low numbers of circulating red blood cells reflected in low HGB and HCT [8]. WBC is elevated on average on admission probably due to the initial initiation of systemic inflammation causing mobilization of leukocytes [9]. WBC then starts to decrease over the next few days after admission. This may be caused by migration of leukocytes from the plasma to injured tissues and skin, decreased chemotactic speed of leukocytes, such as neutrophils, to replenish plasma concentrations, and suppression of granulocyte production by the bone marrow [10–13]. PLT also decreases early following a severe burn injury. By the 4th day after injury the mean PLT are a little over 50% of the admission level. The decrease in PLT following a severe burn is thought to be due to a couple of factors. First, burn injury may cause a change in platelet kinetics causing an increased migration and utilization of circulating platelets [14,15]. Second, following a severe burn, an increased level of fibrinogen may be present causing increased platelet aggregation which can result in a decrease plasma levels of platelet [16].

Although survivors and non-survivors showed similar trends over the first week after injury in several components of the CBC, there were marked significant differences in many components. HGB, HCT, and RCC all showed decreasing values during the first week after burn injury for both survivors and non-survivors. However, non-survivors had significantly lower measurements of HGB, HCT and RCC every day from admission to day 7. This trend also occurs in RDW and may provide an explanation for this finding. RDW reflect red blood cell volume and is an index that measures the variability of red blood cell volume [6]. Increased RDW is thought to be due to altered erythrocyte homeostasis resulting in in increased red blood cell death and impaired red blood cell production and may be caused by increased oxidative stress [17]. RDW was significantly higher from admission in non-survivors and this trend continued through the first week. The increase in RDW may indicate increased red blood cell fragility causing increased red blood cell death and thus causing an even more

Table 3 – Mean values of hematologic parameters. (WBC—white blood cell count (k/mm^2), HBG—hemoglobin (gm/dl), HCT—hematocrit (%), PLT—platelets (k/mm^2), RCC—red cell concentration m/mm^3, RDW—red cell distribution width (%), MPV—mean platelet volume (um^3), MCV—mean corpuscular volume (um^3), MCH—mean corpuscular hemoglobin (pg), MCHC—mean corpuscular hemoglobin concentration (%)).

Day	WBC	HGB	HCT	PLT	RCC	RDW	MPV	MCV	MCH	MCHC
1	19±8	15±2	45±7	232±89	4.9±0.8	14±1.3	8.5±1	92±6	31±2	34±0.7
2	10±6	14±3	42±8	170±56	4.6±1	14±1.3	8.5±1	92±6	31±2	34±0.7
3	5±3	12±3	35±8	130±56	3.8±0.9	14±1.2	8.4±1	92±5	31±2	34±0.7
4	5±3	10±2	30±6	123±51	3.3±0.7	14.6±1.6	8.3±1	91±5	31±2	34±0.7
5	6±3	9.6±2	28±5	139±60	3.1±0.6	15±1.7	8.2±1	91±5	31±2	34±0.7
6	7.5±4	9±2	27±5	166±69	3±0.5	15±1.7	8±1	91±4	31±1.7	34±0.6
7	10±5	9±2	27±5	202±81	3±0.5	15±1.7	8±1	91±4	31±1.7	34±0.6

Table 4 – Comparison of mean WBC, HBG, HCT, and PLT between survivors and non-survivors. (WBC—white blood cell count (k/mm^2), HBG—hemoglobin (gm/dl), HCT—hematocrit (%), PLT—platelets (k/mm^2)).

	WBC			HGB			HCT			PLT		
Day	Lived	Died	p-Value	Lived	Died	p-Value	Lived	Died	p-Value	Lived	Died	p-Value
1	18±8	20±7	0.27	15.2±2	14±3	0.003	48±7	40±8	0.002	233±89	226±89	0.72
2	10±5.5	10±5.9	0.87	15±2.5	11.7±3	0.0001	44±7	35±10	0.0001	178±73	132±51	0.007
3	4.9±2.8	6.8±5	0.01	12±2.5	10±2.7	0.0006	36±7	30±8	0.0005	135±57	103±40	0.02
4	4.8±2.5	6.1±4	0.04	10.5±2	9±2	0.003	31±6	26±6	0.003	128±51	97±39	0.01
5	5.7±2.9	6.4±4	0.37	9.9±1.8	8.4±1.4	0.0004	29±5	25±4	0.0006	146±59	104±48	0.003
6	7.3±3.7	8.6±5.2	0.19	9.6±1.7	8.3±1.3	0.003	28±5	24±4	0.003	175±66	116±63	0.0002
7	9.5±4.6	10.7±5	0.3	9.4±1.7	8.4±1.3	0.01	28±5	25±4	0.01	213±75	140±81	0.0001

profound decrease in HGB, HCT, and RCC in non-survivors. RDW may also reflect an increase in oxidative stress in non-survivors and may be a marker for worse outcomes. In critically ill septic patients, increased RDW on admission has been shown to be a superior marker for predicting mortality than established clinical scores [18]. A large retrospective review of trauma patients showed that admission RDW was an independent predictor of mortality [19] (Tables 3–5).

Another significant difference between survivors and non-survivors were PLT. On admission, PLT were similar between survivors and non-survivors and also decreased over the first 4 days following injury in both groups. However the decrease in PLT was significantly more each day from days 2 to 4 for non-survivors. Additionally, although PLT increased on days 5–7 for non-survivors, the levels were significantly lower than survivors on each day. This finding is similar to several other findings that indicate that non-survivors of a severe burn injury have a lower nadir of PLT compared to survivors and may be a predictor for survival [20,21]. MPV may also be an indicator of survival in burn patients. MPV was similar between survivors and non-survivors from admission to day 5. On day 6 and 7, MPV was significantly higher in non-survivors and the day 7 MPV was independent risk factor for death (O.R. 2.01). The elevated MPV in non-survivors correlates to evidence that mortality is elevated in critically ill patients in the first 3 days after admission [22]. While a causal relationship between elevated MPV and increased mortality has not been elucidated, it may be that non-survivors have younger circulating platelets reflected in a higher MPV. These younger platelets may trigger immune responses and inflammation. Additionally, these younger platelets may also initiate more thrombotic events [7].

There are several limitations of this investigation due to the retrospective nature of the study. First, we did not address the role of blood product transfusion on the measurement of CBC. Our burn unit uses a guideline to transfuse for HGB less than 7 gm/dl [23]. For PLT, our threshold for transfusion is less 20 k/mm^3 for non-surgical situations and 50 k/mm^3 for surgical or bleeds situations [21]. In the ICU, we transfuse fresh frozen plasma if the patient has clinical signs of acute bleeding and has an INR greater than 1.5 IU. If the patient does not have clinical signs of bleeding than transfusion of FFP is reserved for an INR greater than 2.0 IU. In the peri-operative period transfusion of FFP is reserved for an INR greater than 1.5 [24]. While we believe these guidelines were mostly followed, we do not know if transfusions of blood or platelets were given for other clinical reasons. Second, we also did not examine the impact of transfusion during surgical procedures during that first week after admission. It is possible that transfusions or blood or platelets during the first week would have an impact on CBC measurements. Our study was not designed to answer this question as we would have to specifically isolate and match patients who received blood from those who did not. This would create a bias since those patients who did not receive blood may be less severely injured than those who did. Additionally, the number of blood transfusions or the frequency of blood and platelet transfusions during hospitalization may also contribute to changes in RDW and MPV. Third, we did not analyze the impact of medications, such as heparin, on CBC measurements. Given these limitations, we do show that there is a time dependent trend in CBC measurements

Table 5 – Comparison of RCC, RDW and MPV between survivors and non-survivors. (RCC—red cell concentration m/mm^3, RDW—red cell distribution width (%), MPV—mean platelet volume (um^3)).

	RCC			RDW			MPV		
Day	Lived	Died	p-Value	Lived	Died	p-Value	Lived	Died	p-Value
1	5±0.8	4±0.9	0.0005	13.7±1	14.7±2	0.0006	8.4±1	8.6±1	0.57
2	4.8±0.9	3.7±1	0.0001	13.9±1	15±1.5	0.0001	8.5±1	8.6±1	0.7
3	4±0.8	3±0.9	0.0003	14±1	15±1.2	0.0001	8.4±1	8.5±0.8	0.6
4	3.4±0.7	2.6±0.6	0.001	14±2.5	15.5±1.6	0.001	8.3±0.9	8.6±0.9	0.1
5	3.2±0.6	2.7±0.4	0.0002	14.7±1.6	16±2	0.001	8.2±0.9	8.5±0.8	0.15
6	3.1±0.5	2.7±0.4	0.001	15±1.6	16±1.9	0.01	7.7±0.8	8.6±1.1	0.001
7	3.1±0.5	2.7±0.4	0.004	15.3±1.6	16.2±1.9	0.03	7.7±0.8	8.6±1.3	0.00001

following a severe burn injury. These trends may be able to be used to create burn-injury specific reference values. These injury specific reference values may be beneficial to clinically determine whether the change in CBC measurements for a burn patient is following an expected course. Also, determining trends and developing reference values for survivors and non-survivors may help clinicians determine the current clinical trajectory for burn patients.

5. Conclusion

There is an early burn-injury specific trend in the components of a CBC that is a result of severity of the burn injury. These trends can be used as references to determine if a patient's clinical hematologic course is within the expected ranges. Also, there are subtle but specific differences over the first week after injury in the CBC components between survivors and non-survivors. This information may be helpful in determining the clinical trajectory of a burn patient. Finally, components such as RDW and MPV may be biomarkers for severity of inflammation and risk factors for death. Further research is needed to fully understand the utility of RDW and MPV in the treatment of severely burned patients.

Authors' contribution

1. Soman Sen—study design, data collection, data analysis, manuscript writing.
2. Luke Hsei—data collection.
3. Nam Tran—study design, manuscript editing.
4. Kathleen Romanowski—manuscript editing, contribution to discussion.
5. Tina Palmieri—manuscript editing, contribution to discussion.
6. David Greenhalgh—manuscript editing, contribution to discussion.
7. Kiho Cho—study design, manuscript editing.

All of the above listed authors have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

Conflict of interest

There are no conflicts to declare for the any of the authors.

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