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Is Platelet Decline a Predictor of Poor Outcome in Severely Burnt Patients? A 5 Year Retrospective Study

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Purpose: To determine if changes in platelet count after a severe burn injury can be used as a predictor of outcome.

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Abbreviations: ICU, intensive care unit; PPD, percentage platelet decline; OR, odds ratio; APACHE-II, Acute Physiology And Chronic Health Evaluation II score; ROC, receiver operating characteristic; TBSA, total body surface area burn percentage.

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Results: Three hundred and fifty patients were included. The mean total body surface area burn percentage (TBSA) was 29.6%. The majority of patients suffered from flame burns. Overall mortality rate was 43.1%. The nadir in platelet count was on day 3 or day 4. PPD on day 3 (PPD3) >40% and any PPD on day 10 (PPD10) were predictors of mortality with odds ratios of 3.0 and 7.7 respectively.

Conclusion: A PPD3 > 40% and any PPD10 are predictors of increased risk of mortality.

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1. INTRODUCTION

It is well established that thrombocytopenia is common among intensive care unit (ICU) patients, irrespective of the disease process necessitating ICU admission [1-4]. Of significance, is the increased duration of stay, morbidity and mortality associated with thrombocytopenia [5-7]. While some patients are admitted to the ICU with thrombocytopenia, due to their critical illness, others will develop thrombocytopenia during their ICU stay. In the latter group of patients, this

drop in platelet count has been postulated to be a prognostic indicator of sepsis [8]. The percentage decline rather than the absolute platelet counts has been shown to be a significant predictor of mortality [5]. The mechanism causing thrombocytopenia in septic patients is thought to be due to one or more of the following: bone marrow suppression (due to septicemia or hemophagocytosis), increased peripheral consumption and destruction or sequestration of platelets in the spleen [9-10].

In addition to sepsis, drugs (e.g. heparin) and intravascular devices (e.g. central venous catheters), both commonly used in ICU patients, have also been identified as common risk factors [11]. A recent study by Akinosoglou et al. talks about the future use of antiplatelet agents to address thrombocytopenia in septic ICU patients [12]. However, it is the cause of the thrombocytopenia rather than the thrombocytopenia itself that should be focused on. Vander schueren et al. suggested that thrombocytopenia is a risk marker rather than a cause of mortality [1].

Minimal research focusing on platelet count changes in the burn patient have been conducted. In 1944, Macdonald et al. first documented a significant drop in platelet count in patients with burn injuries [13]. The predominant cause is the activation of the coagulation cascade both locally, at the burn wound site, and, distally in organs such as the kidneys and lungs [9]. This leads to the formation of multiple micro-thrombi, which cause consumption of platelets [9]. The nadir of the platelet count is expected to be between day 3 and day 4 post burn injury [9,14-15]. Thrombocytosis following a period of thrombocytopenia is a commonly observed phenomenon which is thought to be due to either a reactive response to the burn injury or a rebound effect of the bone marrow secondary to increased platelet destruction and consumption [14-16]. By day 10 to day 14, platelet counts are expected to have at least normalized [9,15-16]. The extent of the burn injury may also influence both the early development of thrombocytopenia, along with, a less marked subsequent rebound thrombocytosis according to a recent study of pediatric burn patients [17].

The burn patient differs markedly from the general ICU patient in that routinely accepted markers of sepsis such as inflammatory markers and rising

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temperature are often already raised due to the burn injury itself [18]. The difference is so marked that the American Burn Association felt the need for a modified definition of sepsis for the burn patient [18]. If these raised parameters are assumed to be due to sepsis, inadequate use of antibiotics is a potential pitfall. Therefore, if the hypothesis that percentage of platelet decline (PPD) predicts poor outcome is correct, this marker will initiate early action to identify the causative factor for the thrombocytopenia. If PPD is an early indicator of sepsis, blood cultures can be taken promptly and empiric antimicrobials commenced. This is in keeping with the latest surviving sepsis guidelines [19]. Reducing the time to diagnosis of severe sepsis is thought to significantly reduce mortality from sepsis-related multiple organ failure [20].

a) Aim

The aim of this study was to determine if changes in platelet count after a severe burn injury could be used as a predictor of increased risk of mortality.

II. MATERIAL AND METHODS

a) Study setting

The Chris Hani Baragwanath Academic Hospital (CHBAH) Adult Burns Unit (ABU) is a specialist burns unit that receives patients mainly from the Gauteng province of South Africa (population size: 12.2 million) [21]. The burns unit is divided into a 4 bed ICU section and a burns ward consisting of 20 beds. The unit is run by surgeons. General surgeons in training, plastic surgeons in training and surgical interns rotate through the unit on a 4-6 monthly basis under the strict supervision of two specialist burns surgeons. On a weekly basis, an intensivist from the hospital's main ICU will review all patients in the ABU ICU and advise on necessary changes in management.

The unit admits about 200 patients per year. Mortality rate is about 25%. Accidental burns accounts for about 75% of admissions; the remaining cases are often secondary to assault, arson and acid splashes. On average, the total percentage body surface area burnt (TBSA) of patients admitted to the unit ranges between 1 and 59% (unpublished data: personal communication). Most burn injuries above 60% are fatal in our setting. The nurse-patient ratio for the ICU section is kept strictly at 1:1. Each patient is nursed in a separate cubicle. The criteria for admission to the ICU are: TBSA over 20% and/or presence of inhalational injuries. Infection control measures are adhered to, including hand washing prior to entering the cubicles and on leaving the cubicles. Procedures such as daily bathing, dressing changes and line insertions are performed under aseptic techniques. However, there is no written infection control policy specific to the burns unit. The burns ward consists of 5 cubicles, each comprising 4 beds with a nurse-patient ratio of 1:4. These patients

are relatively more stable, have less severe burn injuries and require a lower level of care. In contrast to the ICU patients, these patients have their dressings changed in two dedicated dressing rooms.

b) Study design

This is a retrospective descriptive study analyzing demographic, hematological (platelet count) and microbiological data of adult patients admitted to the CHBAHABU ICU in Johannesburg, South Africa between the 1st January of 2009 and the 31st December 2013.

The following categories of patients were excluded: (1) patients stepped up from the general burns ward to ICU during their admission, (2) patients that died within 2 weeks of admission, including patients that died within 24 hours of admission, (3) patients whose data were not accessible or incomplete due to clerical errors and, (4) patients with thrombocytopenia on admission. Ethical clearance was obtained from the Ethics Committee of the University of Witwatersrand (study number: M140391). The following information on patients admitted to ICU were collected from the admissions register of the unit: age, gender, length of stay, death post admission (number of days post admission after which the patient died), Total Body Surface Area burn percentage (TBSA), mechanism of burn. The National Health Laboratory Service (NHLS) database was accessed using the patient's hospital number to obtain the platelet counts for the first fourteen days of admission. The date of any positive microbiological culture results was collected. Platelet decline was calculated as a percentage of the admission platelet count. No clinical records such as hospital files or ICU charts were reviewed. This study only looked at results that could be retrieved from the laboratory database.

c) Statistical analysis

Data is presented as numbers, percentages, mean (\pm SD), median (25th and 75th quartiles) as appropriate. Continuous data was compared using the t-test if normally distributed or the Mann-Whitney test if not normally distributed. Comparison of categorical data was performed using the Chi-square test. Receiver Operating Characteristic (ROC) curves were constructed. All statistical tests were 2-tailed, and p values < 0.05 were considered significant. Statistical calculations were performed using Microsoft Excel for Mac 2011, Addinsoft XLSTAT Version 2014.4.06 and IBM SPSS Statistics Version 20, release 20.0.0.

The Percentage of Platelet decline (PPD) was calculated as follows: $100 - \left[\frac{\text{platelet count on day X}}{\text{platelet count on admission}} \times 100 \right]$. Thrombocytopenia (clinical thrombocytopenia) was defined as a platelet count $< 100 \times 10^9/\text{l}$. Day 0 was

defined as the day of the burn injury and the day of admission.

III. RESULTS

In this study, a total of 388 patients were admitted to the adult burns ICU in the 5-year period. Of these, 350 were included. The remaining 38 were excluded based on the criteria mentioned previously. The study group consisted predominantly of adult patients between 18 and 49 years of age with a greater proportion being males (61.1%; male: female ratio). Mortality was significantly higher among the group with a higher TBSA ($p < 0.05$). Sepsis, on the other hand, was of similar occurrence among survivors and non-survivors. Table 1 illustrates the basic demographic data of the study population along with univariate analysis.



a) Absolute Platelet Counts and Trend

Following the burn injury, a drop of platelet count was observed followed by a rebound. The nadir in platelet count was on day 3 and by day 10 most survivors had normal platelet counts. The trend of

platelets following admission is shown in Figure 1. The difference in platelet counts on admission and on day 3 post admission between non-survivors and survivors is illustrated in Table 2. The difference was statistically significant on day 3 but not on admission.

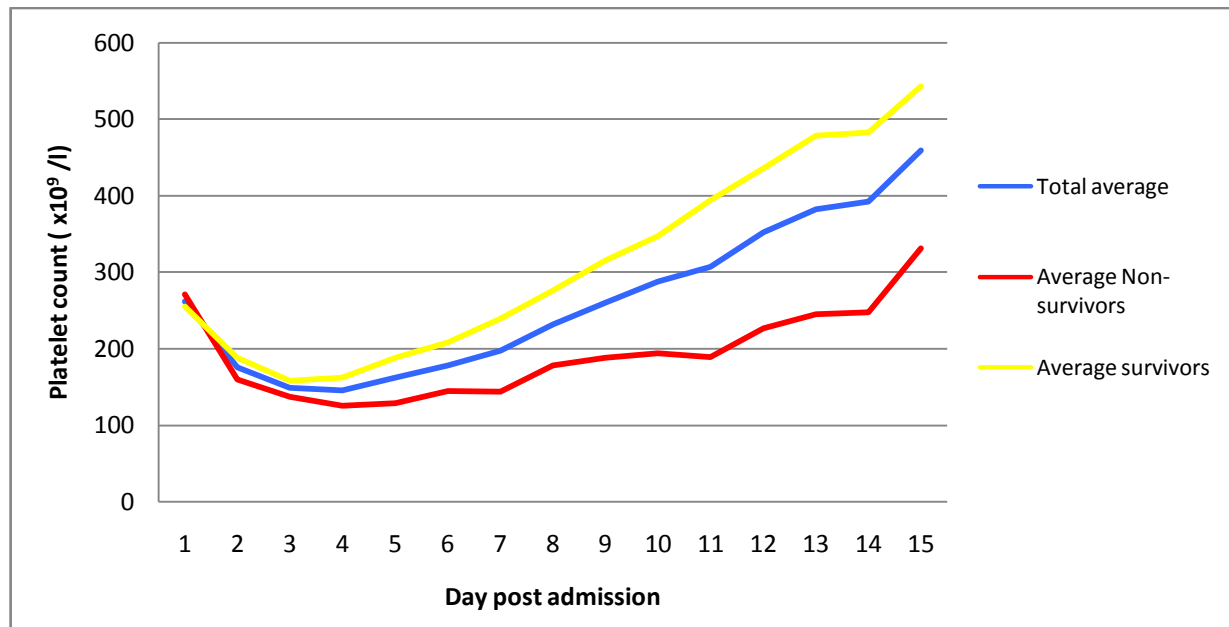


Figure 1: Trend of platelets – Platelet count vs. Day post admission. (The blue line depicts the average trend of platelet count for all patients included in the study. (n=350), the red line refers to the average trend of platelets among non-survivors only (n=151) and the yellow line shows the change in platelet count for survivors (n=199))

Table 2: Platelet counts (x10⁹/l)

	Admission		Day 3	
	Non-Survivors	Survivors	Non-Survivors	Survivors
Median	271.3	255.1	118.5	147
1 st quartile	183.3	181.3	74.7	105
3 rd quartile	316.5	292.3	152	199
p-value (Mann-Whitney ^a , t-test ^b)	0.35 ^a		<0.001 ^b	

b) Percentage Platelet Decline (ppd)

The PPD was then calculated on day 3 and day 10 post admission. Since not all patients had platelet counts on day 0, day 3 and day 10, the sample size for analysis of platelet decline was much lower than 350. 182 patients had counts on both day 0 and 3 allowing for an evaluation of their platelet decline. Table 3 illustrates the statistical difference between the PPD on day 3 (PPD3) and day 10 (PPD10), between survivors and non-survivors.

Table 3 : Percentage platelet decline

	PPD3		PPD10	
	Survivors	Non- Survivors	Survivors	Non-Survivors
Median	37%	53.8%	30.9%	-38.9%
1st Quartile	10.7%	34.1%	-8.7%	-105.9%
3rd Quartile	54.7%	65.4%	59.5%	-5.4%
p-value (Mann-Whitney test)	<0.01		<0.01	

c) *Percentage Platelet Decline on Day 3 (ppd3)*

Comparing the distributions of PPD3 for non-survivors against survivors using the Mann-Whitney test showed a statistical difference with a p-value = 0.000096. The Mann-Whitney test was used because the two distributions were not normally distributed. Using the cut-off of PPD3 > 40%, the following 4 categories were analyzed, non-survivors with PPD3 >

40%, non-survivors with PPD3 < 40%, survivors with PPD3 > 40%, survivors with PPD3 < 40%.

The odds ratio of non-survival with a PPD3 > 40% was calculated to be 3.01 (95% C.I.: 11.6-5.6), sensitivity: 73%, specificity: 53%, positive predictive value: 56%, negative predictive value: 70%. A Receiver Operating Characteristic (ROC) curve for PPD3 is illustrated in figure 2.

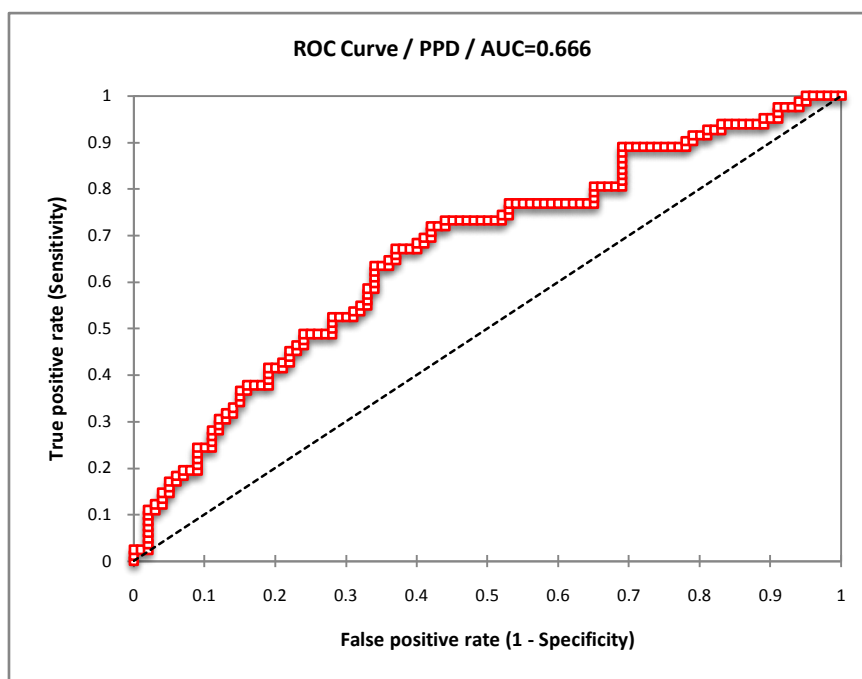


Figure 2: Receiver Operating Characteristic (ROC) curve for PPD3

PPD3 was then analysed against sepsis but was not found to be a predictor, odds ratio:0.45.

d) *Percentage Platelet Decline on day 10*

By day 10 post admission, platelet counts are expected to have normalized. Therefore, PPD is expected to be negative, because it would in fact be a gain. Using the cut-off of PPD of 0%, a Mann-Whitney test revealed a statistical significance (p-value < 0.05) between non-survivors and survivors. The odds ratio of non-survival if PPD10 is more than 0% (any decline) was 7.73 (95% CI: 0.20-0.38), sensitivity: 65.9%, specificity:

80%, positive predictive value: 70.3%, negative predictive value: 76.2%. A ROC curve for PPD10 is illustrated in figure 3. PPD10 was then analysed against sepsis but was not found to be a predictor, odds ratio:0.96.

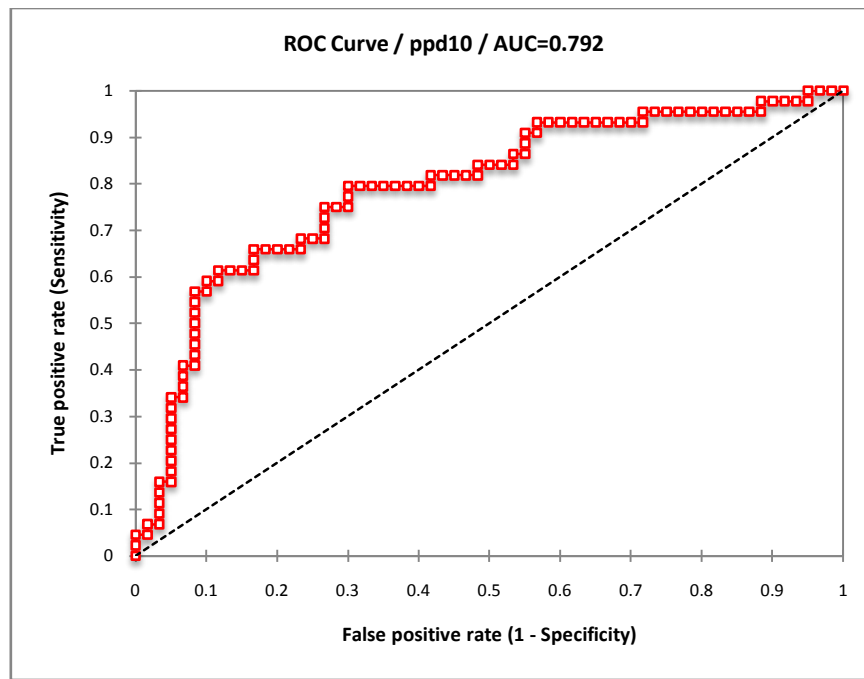


Figure 3 : Receiver Operating Characteristic (ROC) curve for PPD10

IV. DISCUSSION

This study has re-emphasized several known facts regarding severe burn injuries. Higher TBSA and increasing age were shown to be statistically significantly associated with increased mortality. Admissions platelet counts were normal in most patients and there was no statistical difference between the non-survivors and survivors in contrast to a study done by Fenget al. [22]. Taking into account that burn injuries cause a marked reduction in platelets, we hypothesize that these normal admission values could in fact be falsely reassuring and actually be secondary to post burn hemoconcentration. In accordance with the literature, the trend of platelets was seen to be an initial steady drop in all patients with the nadir of the platelet count being between the third and fourth day post admission [9,14-15]. Of note, non-survivors exhibited a more pronounced decline in platelets.

Several mechanisms have been postulated to explain the observed thrombocytopenia. The activation of the coagulation cascade both locally, at the burn wound site, and, distally in organs such as the kidneys and lungs is one of the most favored concept [9]. This leads to the formation of multiple micro-thrombi, which causes consumption of platelets [9]. Another possible contributing factor is the dilutional effect of resuscitation fluids that often follows the period of post burn hemoconcentration. The dilutional effect of intravenous fluids would then cause an iatrogenic thrombocytopenia. However, conflicting with this theory is the fact that the thrombocytopenia seems to persist even after withdrawal of intravenous fluids [23].

In this study, the platelet counts of non-survivors were consistently below the counts of survivors post admission. Percentage platelet decline was used instead of absolute counts because it has previously been shown to be a better prognostic marker, as well as it removes baseline inter-individual differences [22]. In contrast to absolute counts, using the platelet decline also offers a more dynamic measure. In comparison to the APACHE II score, which can only be calculated on admission, the percentage platelet decline allows for daily re-calculations and therefore is thought to be a better marker of progression. Integrating PPD into other scoring systems could improve accuracy. Furthermore, the APACHE II score has not been validated in burn patients.

To our knowledge, a cut off of 40% has never been used before. In keeping with two other studies, this study showed that PPD is a predictor of mortality despite using different cut off values. The results show that a $PPD3 > 40\%$ is an early marker of poor prognosis with an odds ratio of 3.0 but is not a predictor of sepsis (OR: 0.45). Despite being both a known cause of thrombocytopenia and a marker of poor outcome, sepsis in the burnt patients usually occurs several days after the nadir of platelet counts (day 3).

We postulate that a high PPD could be a marker of severity of the burn injury. A high PPD3 should alert clinicians to re-assess their patient. Even though TBSA and PPD were not compared in this study, there might be an association between these two variables. We suggest going back to the history to look for missed comorbidities and re-examining the patient from head to toe for missed injuries. Of prime importance would be a

re-calculation of the TBSA. The PPD10 is another useful predictor of mortality, albeit, only obtainable at a later stage. By day 10, platelet counts should have normalized. The results of this study show that PPD 10 has higher statistical power than PPD3, with an odds ratio of 7.7 and higher specificity for mortality, but again, is not an indicator of sepsis.

There are several limitations to this study. The study design is retrospective in nature, and as such it limits the amount of information obtainable regarding patients. This study was a review of information obtainable from the laboratory database only; patient records and ICU charts were not reviewed. As a result, this introduces a serious limitation, which is the inability to analyze some important variables that could have affected platelet counts. These are: (1) transfusion of blood components (red cell concentrate, platelets, fresh frozen plasma), (2) medication given to patients, heparin, morphine, silver sulphadiazine and paracetamol are some of many drugs known to cause thrombocytopenia, (3) pre-existing co-morbidities such as HIV positivity, chronic renal disease and liver disease, (4) volume of intravenous fluids, and (5) surgical procedure performed. It is, however, unlikely that survivors received a different management to non-survivors.

Lastly, multivariate logistic regressions were not performed.

V. CONCLUSION

Higher TBSA and increasing age are predictors of poor outcome in burn patients. This study suggests that a PPD3 of more than 40% and any value for PPD10 are also predictors of increased risk of mortality with an odds ratio of 3.0 and 7.7 respectively. A high PPD3 should prompt a re-evaluation of the patient. There is scope for a prospective study to evaluate the prognostic value of PPD with special attention to all possible variables that may affect platelet counts.

Conflicts of interest:

The authors report no conflict of interest.

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