Platelet Counts in Early Trauma Care, Prague, 22 November 2016

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[Figures and Tables included in attached PowerPoint File in the order mentioned in the text]

Founded in 1968, the R Adams Cowley Shock Trauma Center associated with the University of Maryland in Baltimore, Maryland, USA, was the first and is still among the most active civilian trauma centers in the world. The idea that specialized centers like this were needed emerged in the 1960's, with the observation, in the US at least, that high-speed motor vehicle injuries, urban gun violence, and slow and inept patient transport were costing lives. So the organizing principles of the civilian trauma center movement became 1) coordinated, well-trained military-style casualty evacuation systems and 2) regionalized centers with specialized trauma teams led by senior physicians on site at all times.

Maryland Shock Trauma admits 7 – 8,000 patients a year, about 5,000 of them directly from the scene of injury from a fairly dense base of slightly more than half the population of the Czech Republic and slightly less than half its geographic area.

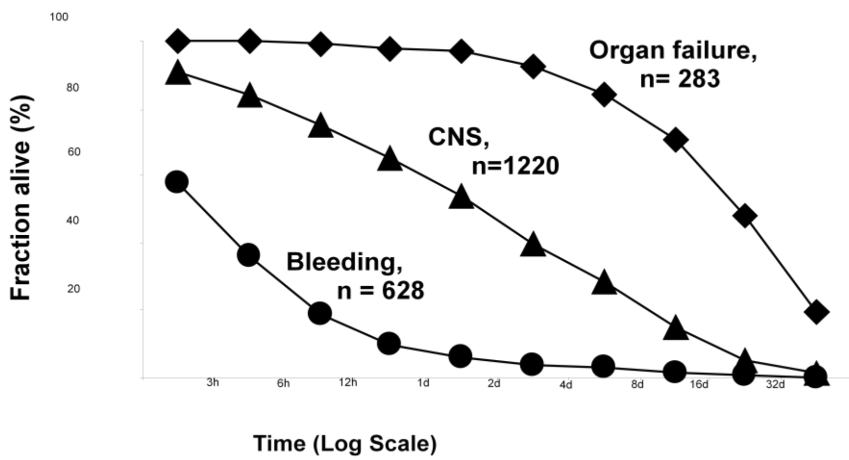
In the 1970's and '80's, with the growth of large regional trauma centers and the increasing availability of fast and user-friendly computer systems, we were now able to record, track, and systematize vast amounts of individual patient data to explore patterns of injury, care, and outcomes. Many countries, like the Czech Republic, now have national Trauma Registries and large institutions like Maryland Shock Trauma also build and maintain their own registries that are representative enough of a population's experience to yield useful insights.

The first big study I was involved in at Shock Trauma was a look at a 12-year history of admissions to our center, 1997 – 2008 (Dutton et al, 2010). The span of dates was chosen for two reasons: 1) Our Trauma Registry data collection system was fully automated over that period, with no obvious gaps, and 2) by 2003, the beginning of the second 6 years, our Trauma Resuscitation protocol was fully committed to hemostatic resuscitation. So our research question was, are we doing better? Could we document decreased mortality in the second 6 years compared to the first 6 years? Of the nearly 85,000 admissions to Shock Trauma in the study period, about 70,000 were admitted directly from the scene of injury, that is, not transferred from another center, minimizing the time from injury to advanced care. From them, we further selected only those who survived at least 15 minutes after admission. As Dr. Richard Dutton, our lead author, my boss, and chief of trauma anesthesia at the time, put it, "If you're going to evaluate care, caregivers need to have had time to do something."

This gave us a study population of about 68,000 injured people, of whom not quite 3000 died, for a mortality rate of about 4%. This in fact stayed stable over the study period, though we did document worsening injury severity.

But I've always thought that the most important thing that emerged from this study was our graph of time-to-death among those patients who died (Figure 1).

Figure 1: Time to trauma death, major causes, 1997-2008



Civilian and military trauma deaths sort consistently into three general patterns of mortality: those due to multi-organ failure, those due to head injury (CNS, central nervous system), and those due to bleeding. The largest proportion is due to head injury, followed closely by bleeding, and then multi-organ failure, a much smaller proportion. Mean time to death for the three groups is very different, roughly 2 hours for those who die of bleeding, roughly 24-48 hours for those die of head injuries, and up to a week or more for those who die of organ failure. Of those patients who will die of bleeding after severe trauma, we have already lost half of them by the end of the second hour of advanced care.

In fact, this confirms what we've always known. To maximize survival and the preservation of function, we must act early, using the right products for the right situation, and often without laboratory or imaging to support clinical decision-making. So the more we know about what's actually going on in those first minutes and hours is important.

Of the three main blood products at issue here, the most questions remain about platelets. Platelets are always in short supply, expensive, and difficult to handle. Knowing whether they are really needed and when and how to give them is important.

Among the explosion of early studies on balanced resuscitation that were emerging in the mid-late 2000's, was one in 2008 from a large multicenter group that suggested that platelets might have an additional value in decreasing mortality from head injury. (Holcomb et al, 2008) By that time, our Trauma Registry was fully linked electronically with our clinical laboratories, and in 2009, we published a study of a subset, 2000-2006, drawn from our same large trauma population, looking at the results of conventional coagulation tests drawn at the time of admission. (Hess et al, 2009) I will review some of the information from both of these studies below. However, we then decided to look platelet counts not just at admission but through the early hours of care among patients further selected for high risk of bleeding death. This is the study I will be reviewing for you today (Stansbury et al, 2013).

For this study, we included only those patients from our big database—admitted directly from the scene of injury and surviving at least 15 minutes—who had also been given at least one unit of uncrossmatched Group O “universal donor” red blood cells in the first hour of admission. Such units are available at all times in our Trauma Resuscitation Unit and, in our system, their use a key clinical marker for perceived risk of bleeding death—that is, a marker not dependent on laboratory values, imaging, or scoring systems but on the initial impressions of the care teams as the patient is being admitted. Using these criteria, we ended up with a final study group of just fewer than 1300 patients (Figure 2).

Figure 2: Study of platelet counts in the first 24 hours of care: Patient selection

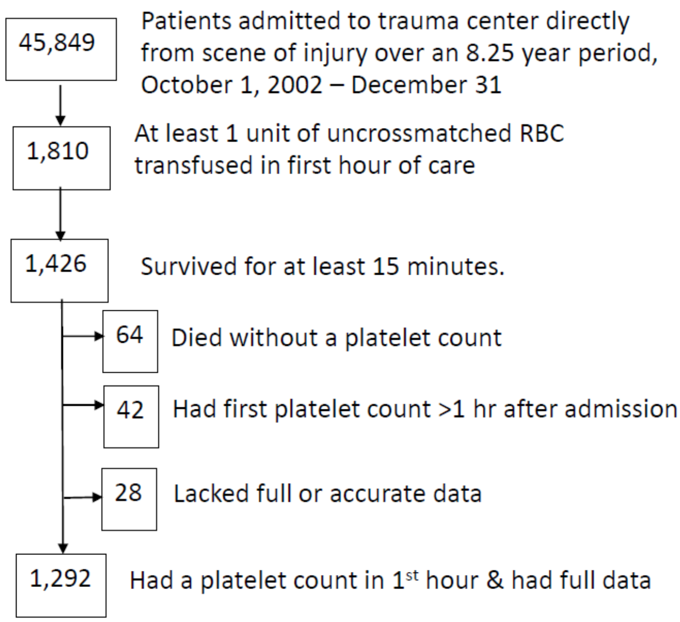


Table 1 summarizes the demographics and injury data of our study group. The mean ages for men and women shown in the table hide the fact that the modal—the most frequent—age for males in our wider trauma population is 18 and the modal age for females is 78. Elderly females account disproportionately for falls and young males account disproportionately for injury due to interpersonal violence—gunshot wounds, stabbings, and blunt assaults.

Table 1: Demographics - Study population by age, sex, injury severity, and cause of injury

	All	Women	Men
Totals	1292	277	1015
Mean Age	40	47	38
Mean ISS	31	33	30
Mean TRISS	0.651	0.610	0.662
Cause of injury			
MVA	744	213	531
GSWs	240	15	225
Falls	83	24	59
Stabbings	167	18	149
Blunt assault	19	4	15
Other/UnK	39	3	36

ISS = Injury Severity Score, TRISS = Trauma Revised Injury Severity Score, MVA = motor-vehicle-associated, GSW = gunshot wound

Remember that ISS or Injury Severity Score is a purely anatomic score, calculated retrospectively—so, of use to epidemiologists but of no use to the trauma team. Trauma Revised ISS or TRISS is also a retrospective score but includes selected vital signs and the Glasgow Coma Score, used as a way to document head injury.

ISS is a cumulative score: 0 is no injury; scores greater than 15 suggest severe injury, scores of 50 and above, to a maximum of 75, record injuries that are rarely survivable. TRISS is expressed as a digital fraction of 1, with scores of less than point 75 suggesting severe injury and those below point 500, rarely survivable. So the mean scores shown in Figure 3 for our study population suggest significant injury, supporting, retrospectively and independently, the initial clinical impressions of the trauma team and the legitimacy of our selection criteria.

Figure 3: Plot of number of units of uncrossmatched pRBC given to study cohort patients versus their admission platelet count.

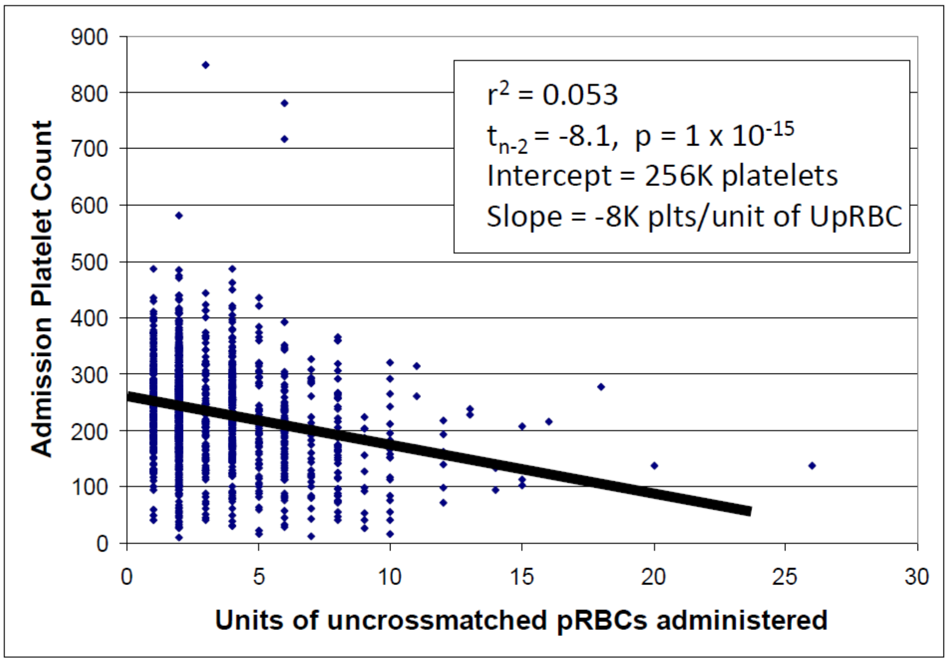


Table 2 summarizes mortality in the study group. Historically, as noted above, bleeding has been the second most common cause of death in our trauma population, so a disproportionate number of deaths in our study group were due to bleeding. Again, not surprising, given the selection criteria for our study group. Among those who died of bleeding, 87% were dead within 12 hours.

Table 2: Study group mortality = 432/1292 patients

	All	Women	Men
Totals	432	101	331
Cause			
CNS	170	40	130
Bleeding	**183**	42	141
MOF	52	9	43
Hours to death	93	64	103

Overall, the mean admission platelet count (calculated from the lowest count for an individual within 1 hour of admission) was 228 x 10^9 /L, thus, slightly less than the conventional lower limit of normal for platelets, usually given as 250 x 10^9/L

Not surprisingly, any way we looked at it, admission platelet counts were closely correlated with degree of injury. Figure 3 shows the negative correlation of lower admission platelet counts with greater number of units of uncrossmatched Group O RBCs given emergently starting in the first hour of resuscitation. Figure 4 shows the negative correlation of decreasing admission platelet counts with increasing Injury Severity Score. Figure 5 shows the positive correlation of increasing admission platelet counts with increasing Trauma Revised ISS.

Figure 4: Plot of the injury severity score (ISS) versus the admissior platelet count in study cohort patients.

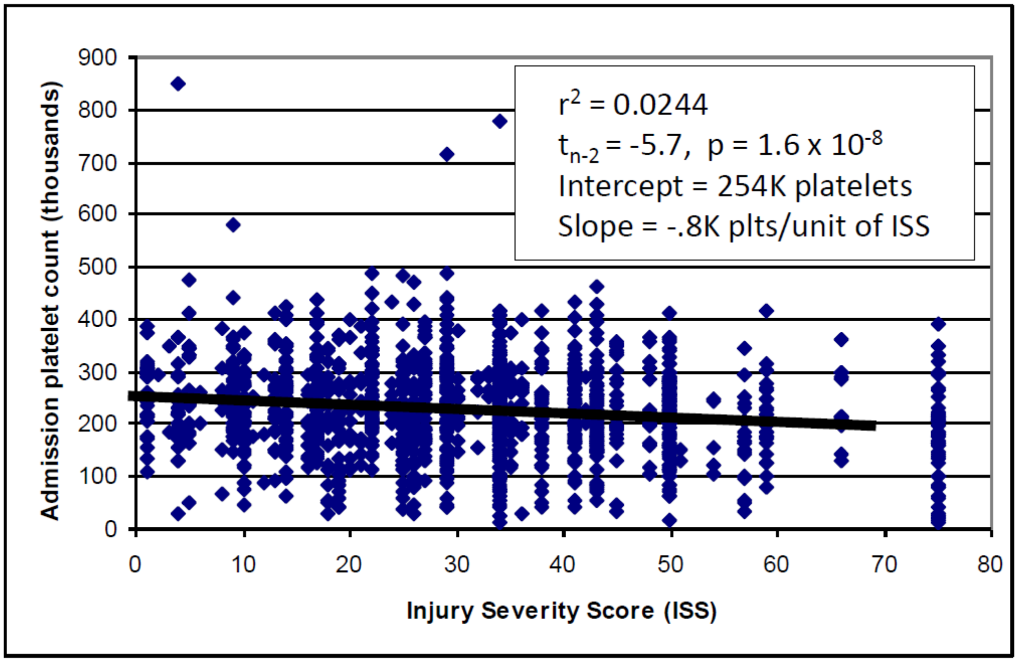
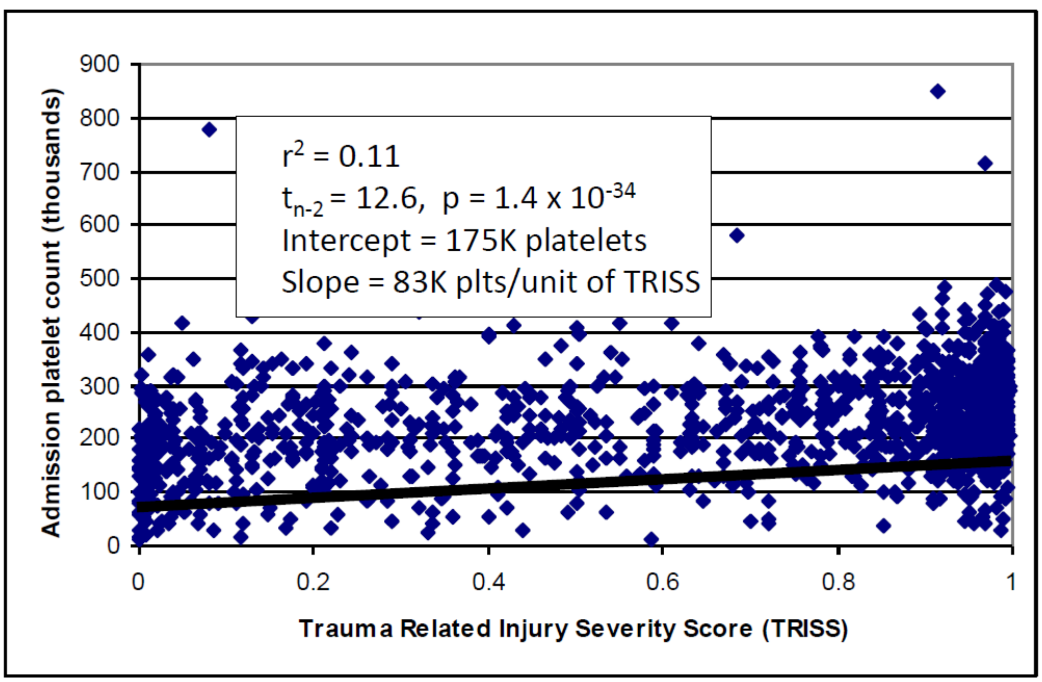


Figure 5:Plot of the trauma revised injury severity score (TRISS) versus the admission platelet count in study cohort patients.



Again not surprisingly, we found a clear relationship between admission platelet count and mortality. Figure 6 shows the step-wise decrease in mortality associated with increasing admission platelet counts. What interests me most in this graph is the relative equivalence of deaths due to bleeding and to head injury in the groups with relatively higher admission platelet counts. Then, in the group with admission platelet counts of 100-150 x 10^9/L bleeding deaths begin to become more frequent than CNS deaths. And then, in the lowest two groups, hemorrhagic deaths are more than twice as common than those due to head injury

Figure 6: Relationship between admission platelet count and in-hospital mortality

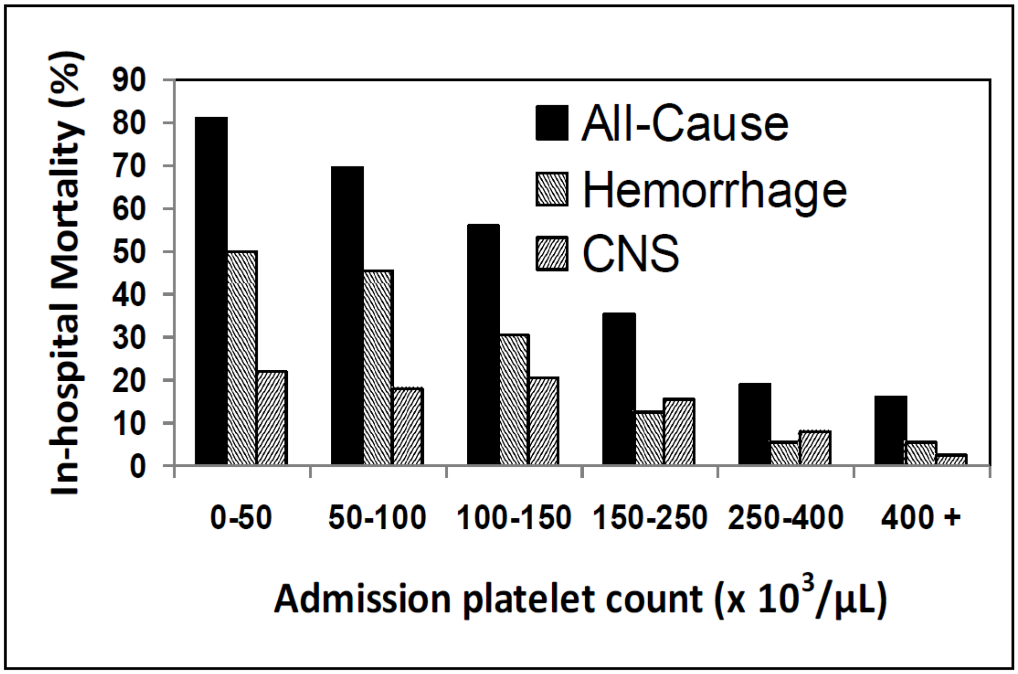


Table 3 shows another view of these same findings, using odds ratios. As admission platelet counts fall below normal parameters, odds ratios for mortality increase.

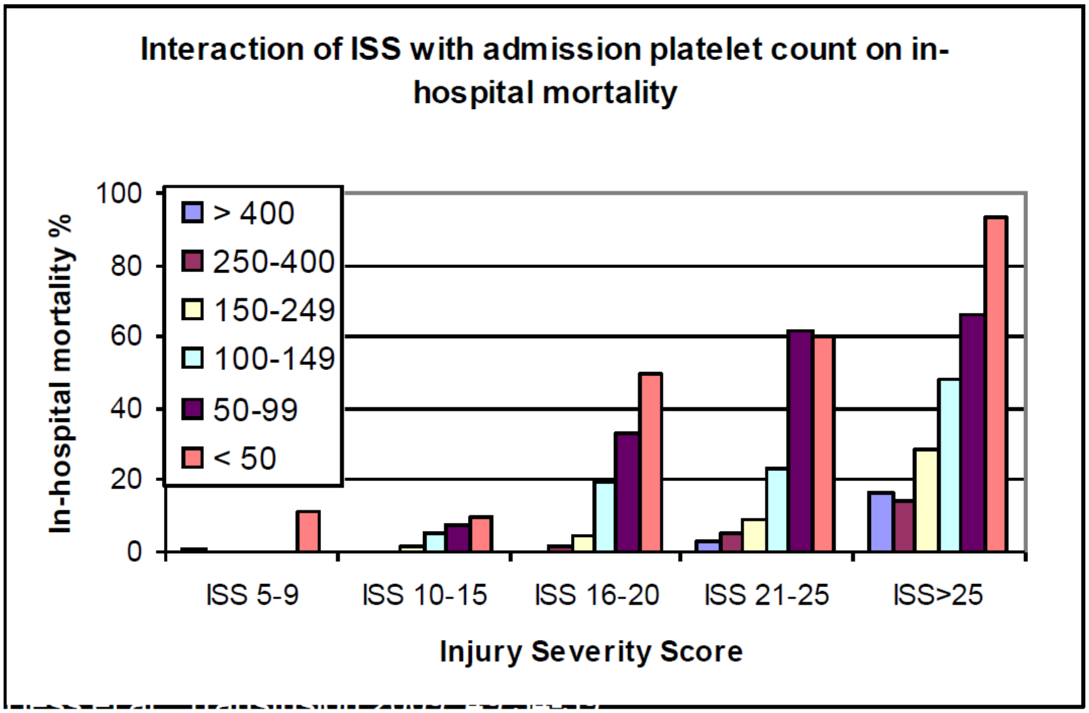
Table 3: Admission platelet count & odds of dying

Admission Platelet count group, K/mcL	Odds of mortality, unadjusted	Odds of mortality, TRISS adjusted
>400	0.8	1.0
250 – 400	1.0	1.0
150 - 250	2.4	1.9
100 - 150	5.5	2.7
50 - 100	9.9	4.2
0 - 50	18.7	8.2

As shown in Figure 6, a kind of flex point appears between 100-150 x 10^9 /L in which the odds of death increase markedly. As I have said before, none of this was a surprise. It also makes sense intuitively.

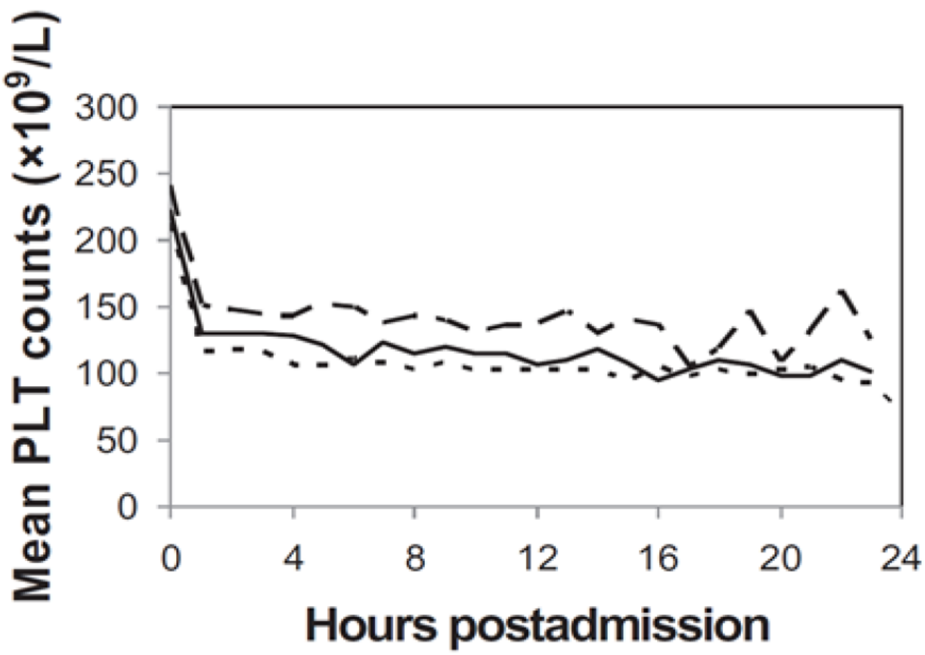
I mentioned our previous study of admission laboratory values for conventional coagulation tests in a general trauma population (Hess et al, 2009). Figure 7 is a figure from that study, showing admission platelet counts shows a similar step-wise progression in mortality with increasingly severe anatomic injury. And within each level of anatomic injury, we see a stepwise progression in mortality among those with lower platelet counts upon admission, with a similar flex-point effect at about 100-150 x 10^9 /L (pale green).

Figure 7:



What was a surprise in our newer study, in a population selected for high risk of bleeding death, was that subsequent platelet counts, drawn by the end of the second hour of care, decreased the overall mean of 228 x 10^9/L ± 90 x 10^9/L at admission to 124 x 10^9/L ± 60 x 10^9/L or roughly 100 x 10^9/L. Beyond that drop, however, mean platelet counts decreased only slightly. These findings were consistent across all categories of anatomic injury (Figure 8).

Figure 8: Mean first and subsequent (up to 24 hours) platelet counts at three levels of injury severity: (– –) ISS less than 17, mild and moderate; (—) ISS 17 to 25, severe; (- - -) ISS greater than 25, profound.



So what does this tell us about what to do about platelets and whether early platelet counts are good guides to therapy in trauma patients at high risk of bleeding death? Certainly, these data suggest that functional platelets are likely to be an important factor in early resuscitation where there is a strong risk of critical bleeding. But beyond that, there are still a lot of questions and a lot of uncertainty.

One of those uncertain areas is so-called "transfusion triggers" for platelets, that is, platelet counts below which patients are felt to be at excess risk of bleeding, either spontaneously, as in thromobocytopenic conditions such as leukemia, or during invasive bedside or surgical procedures. Currently published trigger levels are reasonable but are not as firmly evidence-based as those make demands for products from the blood bank sometimes think. The message must be, treat the patient, not the number.

Part of the uncertainty about appropriate platelet transfusion thresholds is the recognition of the tremendous normal variability in human platelet counts. The genetic component of platelet counts ranges from roughly 50 – 80 percent of the differences we see in normal individuals' platelet counts is due to genetic variations. The Genome-Wide Association Study (GWAS) of platelet count and mean platelet volume in African Americans (Quayyum et al, 2012) identified 10 loci with biologic plausibility to account for variability in platelet expression.

These effects can be seen in on a population basis among large study groups of individuals who volunteer to participate in community surveys rather than being selected from hospital patients or on the basis of other health-related interactions. Table 4 summarizes the results from the 3rd US national Nutritional and Health Examination Survey (NHANES III) done some years ago now but still useful (Segal and Moliterno, 2006). Note that the 50th percentile here among healthy individuals falls at 271 x 10^9/L, at the low end of conventional normal thresholds for platelets.

Table 4: Segal and Moliterno 2006 NHANESIII

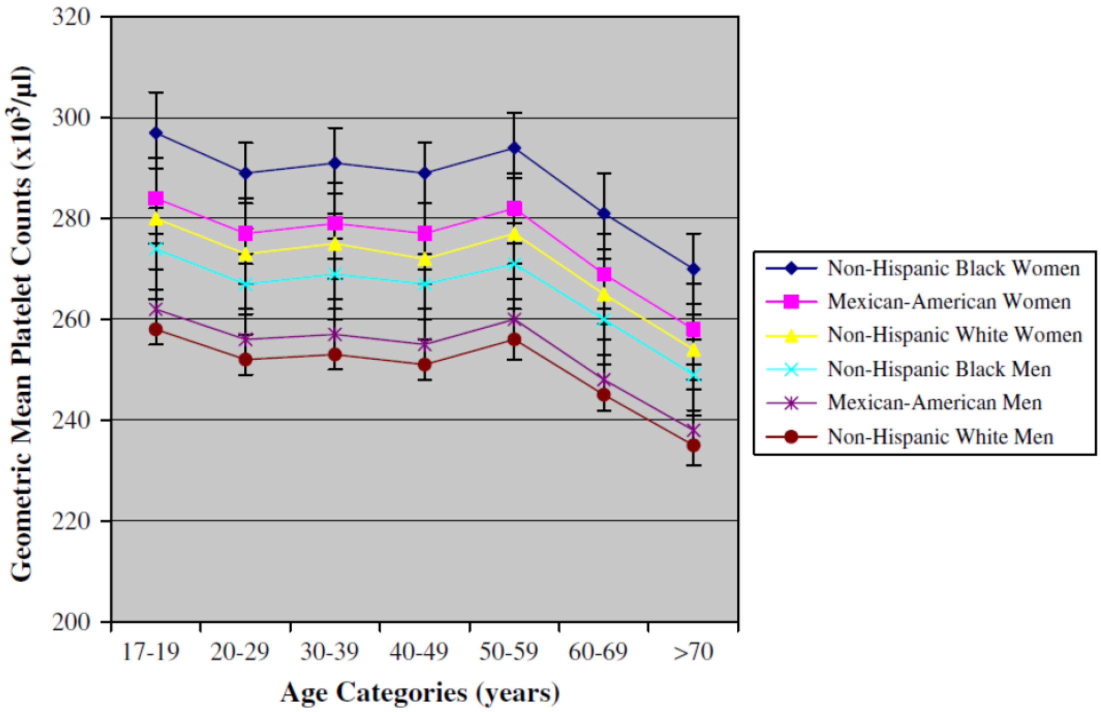
TABLE 2. Distribution of platelet counts for adult participants in the Third Nutritional and Health Examination Survey ($N = 12{,}142$)

Percentile	Platelet count ($\times 10^3/\mu L$)
1	142
10	198
25	230
50	271
75	317
90	364
99	458

Mean = 271
SD = 61
95% normal range 149-393

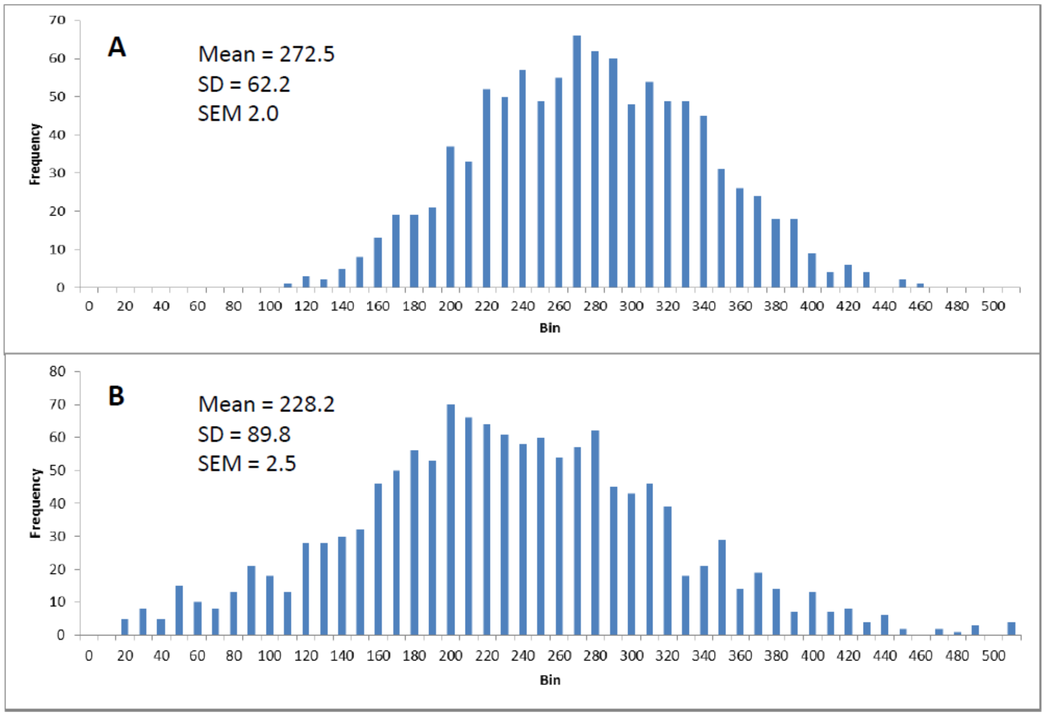
Figure 9, also from the survey report, shows a further breakdown of platelet counts by sex and age with socio-cultural designations, “ethnicity,” used as surrogates for genetic characteristics. "Black” suggests significantly African genetic input; “Hispanic” or “Mexican-American” suggests at least some indigenous Western Hemisphere genetic input; and “white” suggests largely European. The message here is that within the recognized variability of platelet counts, there are distinguishable demographic and genetic subgroups. It is interesting to note that in all groups, males have the lower baseline platelet counts and as well as being the more likely to be trauma patients.

Figure 9: Data from NHANES III, Seagal and Molinaro, 2006: Mean platelet counts by age, sex, and ethnicity



To get at least a tentative look at the interplay of baseline variability versus the effects of early trauma in platelet counts, for our study of platelets in high risk trauma patients, we also pulled a random sampling of platelet counts from the NHANES III data and graphed them against the admission platelet counts from our study cohort (Figure 10). Although the overall patterns are roughly similar, the curve of our data is flattened and skewed to the left. And essentially all of our study patients will experience in the next hour, a decrease of platelet counts of roughly 100 x 10^9/L.

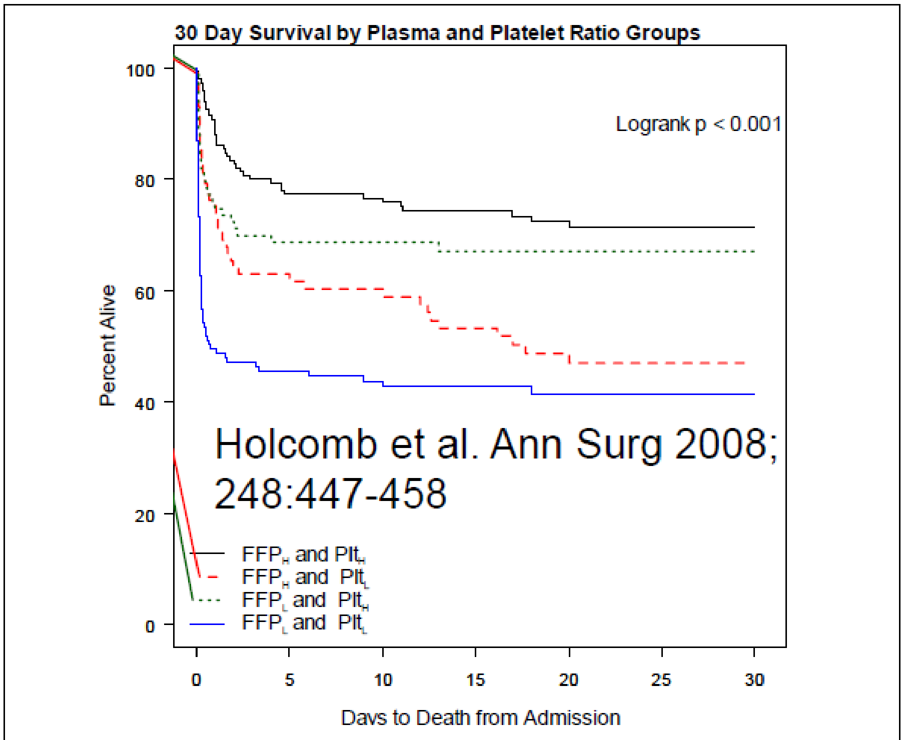
Figure 10: Platelet counts - US normal and after trauma



A) Random sample of 1000 from a normal distribution with 271,000 ± 61,000/μL (NHANES III; Segal and Moliterno, 2006.
B) Admission counts on 1292 trauma patients requiring uncrossmatched RBC in first hour of care.

In truth, as in the debate over transfusion triggers, we're still not sure what platelet counts and platelet repletion mean in the face of trauma. Figure 11 is from the 2008 study I mentioned earlier. This was a large multicenter study of trauma transfusion patterns over 12 months, 2005 – 2006, in 16 civilian trauma centers in the US, done early in the debate on balanced resuscitation. The main focus of the study was on red cell and plasma use in so called "massively transfused" patients, those receiving 10 or more units of red cells in the first 24 hours, but the graph shown in Figure 11 suggested an additional effect of the use of platelets in hemostatic resuscitation. The four lines of the graph correspond to four different survival curves associated with the use of four different combinations of red cells, plasma, and platelets in resuscitation. The blue line at the bottom is the survival curve for trauma patients given significantly more units of red cells than plasma or platelets in the first 24 hours. The broken red line is the survival curve for patients given roughly equal proportions of red cells and plasma but fewer units of platelets. The broken green line is the opposite: higher proportions of platelets with the red cells and relatively fewer of plasma. And the solid line is the use of near-equivalent proportions of all three blood products. What I think we are seeing in the lowest (blue) line, with its sharp early drop in survival and relatively little subsequent change is the early bleeding deaths of patients whose acute coagulopathy of trauma was not treated adequately, whereas the other lines show, by varying degrees of repletion of coagulation factors, the prevention of early bleeding death and so improved survival over the first hours of care but then the subsequent deaths due to head injury 48 – 72 hours into care and then multi-organ failure in the extended tail of the curves.

Figure 11: 30-day mortality, by units of plasma to pRBCs, among 466 massively-transfused trauma patients seen at 16 academic trauma centers



This graph was read as suggesting a possibly additive role for platelet therapy in decreasing mortality from head injury. A subsequent study using data gleaned from many of these same centers (Brasel et al, 2011) suggested a clear advantage, in severely injured patients at high risk of death from bleeding, of increased proportions of platelets, rather than plasma, in treatment of those at additional risk of death from head injury, though the additional plasma transfused with each unit of platelets perhaps confuses the clarity of this finding. Subsequent work has suggest specific abnormalities of platelet function unique to traumatic brain injury and a possible animal model, but many questions remain.

An unexpected consequence of Dr. Bohoněk's kind invitation to speak at this symposium was that, the more I thought about our 2013 study, presented here, the more I wanted to repeat that study in a more recent patient population, now well into the era of hemostatic resuscitation. To confirm our findings if possible, of course. But also to look at the effects of blood product therapy—which we did not do in this study—along with patterns of platelet counts in the first 24 hours of care in our wider population. Are the patterns I showed you here unique to bleeding patients? Are patterns in the general trauma population the same but less pronounced? Are there patterns of platelet count response unique to head-injury patients? Or to blunt versus penetrating injury? I am now in the process of collating the raw data for those analysis and hope perhaps at some future time to be able to share those results with you.

Again, many thanks for the invitation to speak and for your attention.

References:

Brasel KJ, Vercruysse G, Spinella PC, Wade CE, Blackbourne LH, et al. The association of blood component use ratios with the survival of massively transfused trauma patients with and without severe brain injury. J Trauma. 2011 Aug;71(2 Suppl 3):S343-52. doi: 10.1097/TA.0b013e318227ef2d.

Dutton RP, Stansbury LG, Leone S, Kramer E, Hess JR, Scalea TM. Trauma mortality in mature trauma systems: are we doing better? An analysis of trauma mortality patterns, 1997-2008. J Trauma. 2010 Sep;69(3):620-6. doi: 10.1097/TA.0b013e3181bbfe2a.

Hess JR, Lindell AL, Stansbury LG, Dutton RP, Scalea TM. The prevalence of abnormal results of conventional coagulation tests on admission to a trauma center. Transfusion. 2009 Jan;49(1):34-9. doi: 10.1111/j.1537-2995.2008.01944.x.

Holcomb JB, Wade CE, Michalek JE, Chisholm GB, Zarzabal LA, Schreiber MA, Gonzalez EA, Pomper GJ, Perkins JG, Spinella PC, Williams KL, Park MS. Increased plasma and platelet to red blood cell ratios improves outcome in 466 massively transfused civilian trauma patients. Ann Surg. 2008 Sep;248(3):447-58. doi: 10.1097/SLA.0b013e318185a9ad.

Qayyum R, Snively BM, Ziv E, Nalls MA, Liu Y, et al. A meta-analysis and genome-wide association study of platelet count and mean platelet volume in African Americans. PLoS Genet. 2012;8(3):e1002491. doi: 10.1371/journal.pgen.1002491. Epub 2012 Mar 8.

Segal JB, Moliterno AR. Platelet counts differ by sex, ethnicity, and age in the United States. Ann Epidemiol. 2006 Feb;16(2):123-30. Epub 2005 Oct 24.

Stansbury LG, Hess AS, Thompson K, Kramer B, Scalea TM, Hess JR. The clinical significance of platelet counts in the first 24 hours after severe injury. Transfusion. 2013 Apr;53(4):783-9. doi: 10.1111/j.15 J Trauma. 2011 Aug;71(2 Suppl 3):S343-52. doi: 10.1097/TA.0b013e318227ef2d.