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| |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | | **Time (min)** | **30** | **45** | **60** | **67** |  | **6-hour Ratio** | **% Time ≥ 0.75** | **Classification** | | **Plasma** | 0 | 0 | 4 | 5 |  | 0.83 | 10.4% | Off-Target | | **Platelets** | 0 | 0 | 6 | 6 |  | 1 | 32.8% | Off-Target | | **PRBC** | 3 | 6 | 6 | 6 |  |  |  |  | |
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| **Supplemental Figure 1.** Examples of On-Target and Off-Target calculations using prototypical patients from the PROMMTT study. Red boxes are time intervals where the ratio of plasma:PRBC or platelet:PRBC is <0.75, respectively. Plots taken from Figure 1, Holcomb JB, et al. The prospective, observational, multicenter, major trauma transfusion (PROMMTT) study: comparative effectiveness of a time-varying treatment with competing risks. *JAMA Surg*. 2013 Feb;148(2):127-36, with permission. |

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| **Supplemental Figure 2.** Study flow diagram. |

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| A  Chart, line chart  Description automatically generated | B  Chart, line chart  Description automatically generated |
| **Supplemental Figure 3.** Youden’s index analysis to determine optimal ratio and percent time for plasma:PRBC (blue lines) and platelet:PRBC (red lines) for 24-hour survival. A) Optimal ratio for plasma:PRBC was found to be 0.77 while the optimal ratio for platelet:PRBC was found to be 0.75. B) Optimal percent time for plasma:PRBC and platelets:PRBC was found to be 42%. | |

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| **SUPPLEMENTAL TABLE 1.** Number of CAT+ patients at each sliding hour | |
| **Time from Arrival** | **Patients Transfused** |
| 60 min | 277 |
| 90 min | 360 |
| 120 min | 407 |
| 150 min | 447 |
| 180 min | 473 |
| 210 min | 492 |
| 240 min | 501 |
| 270 min | 508 |
| 300 min | 515 |
| 330 min | 520 |
| 360 min | 524 |
| PRBC totals during each 60-minute resuscitation interval were used to identify all CAT+ patients in the PROMMTT cohort for a total of n=524. | |

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| **Supplemental Table 2.** Causes of Death by Time Period for CAT+ Cohort*a,b* | | | | | | | |
|  |  | **Plasma:PRBC** | | | **Platelet:PRBC** | | |
|  | **CAT+** | **Off-Target** | **On-Target** | ***p*** | **Off-Target** | **On-Target** | ***p*** |
|  | **(n = 524)** | **(n = 311)** | **(n = 213)** |  | **(n = 408)** | **(n = 116)** |  |
| **Cause of Death at 24-h** 116 (22.1) | | 83 (26.7) | 33 (15.5) | 0.003 | 103 (25.2) | 13 (11.2) | 0.002 |
| Exsanguination | 86 (16.4) | 64 (20.6) | 22 (10.3) | 0.003 | 77 (18.9) | 9 (7.8) | 0.007 |
| Brain injury | 28 (5.3) | 13 (4.2) | 15 (7.0) | 0.218 | 21 (5.1) | 7 (6.0) | 0.888 |
| Cardiovascular | 28 (5.3) | 21 (6.8) | 7 (3.3) | 0.125 | 23 (5.6) | 5 (4.3) | 0.744 |
| Airway/Respiratory | 7 (1.3) | 4 (1.3) | 3 (1.4) | 1.000 | 5 (1.2) | 2 (1.7) | 1.000 |
| Multi-organ failure | 0 (0.0) | 0 (0.0) | 0 (0.0) | n/a | 0 (0.0) | 0 (0.0) | n/a |
| Sepsis | 0 (0.0) | 0 (0.0) | 0 (0.0) | n/a | 0 (0.0) | 0 (0.0) | n/a |
| Other | 13 (2.5) | 11 (3.5) | 2 (0.9) | 0.111 | 12 (2.9) | 1 (0.9) | 0.351 |
|  |  |  |  |  |  |  |  |
| **Cause of Death between 24-h to 30-d** 53 (10.1) | | 30 (9.6) | 23 (10.8) | 0.778 | 34 (8.3) | 19 (16.4) | 0.018 |
| Exsanguination | 3 (0.6) | 0 (0.0) | 3 (1.4) | 0.131 | 2 (0.5) | 1 (0.9) | 1.000 |
| Brain injury | 26 (5.0) | 14 (4.5) | 12 (5.6) | 0.703 | 18 (4.4) | 8 (6.9) | 0.398 |
| Cardiovascular | 3 (0.6) | 1 (0.3) | 2 (0.9) | 0.741 | 3 (0.7) | 0 (0.0) | 0.819 |
| Multi-organ failure | 19 (3.6) | 13 (4.2) | 6 (2.8) | 0.561 | 13 (3.2) | 6 (5.2) | 0.466 |
| Airway/Respiratory | 9 (1.7) | 3 (1.0) | 6 (2.8) | 0.207 | 5 (1.2) | 4 (3.4) | 0.222 |
| Sepsis | 5 (1.0) | 3 (1.0) | 2 (0.9) | 1.000 | 3 (0.7) | 2 (1.7) | 0.670 |
| Other | 13 (2.5) | 6 (1.9) | 7 (3.3) | 0.487 | 8 (2.0) | 5 (4.3) | 0.272 |
|  |  |  |  |  |  |  |  |
| **Cause of Death at 30-d** 169 (32.3) | | 113 (36.3) | 56 (26.3) | 0.020 | 137 (33.6) | 32 (27.6) | 0.269 |
| Exsanguination | 89 (17.0) | 64 (20.6) | 25 (11.7) | 0.011 | 79 (19.4) | 10 (8.6) | 0.010 |
| Brain injury | 54 (10.3) | 27 (8.7) | 27 (12.7) | 0.183 | 39 (9.6) | 15 (12.9) | 0.378 |
| Cardiovascular | 31 (5.9) | 22 (7.1) | 9 (4.2) | 0.242 | 26 (6.4) | 5 (4.3) | 0.543 |
| Multi-organ failure | 19 (3.6) | 13 (4.2) | 6 (2.8) | 0.561 | 13 (3.2) | 6 (5.2) | 0.466 |
| Airway/Respiratory | 16 (3.1) | 7 (2.3) | 9 (4.2) | 0.302 | 10 (2.5) | 6 (5.2) | 0.231 |
| Sepsis | 5 (1.0) | 3 (1.0) | 2 (0.9) | 1.000 | 3 (0.7) | 2 (1.7) | 0.670 |
| Other | 26 (5.0) | 17 (5.5) | 9 (4.2) | 0.662 | 20 (4.9) | 6 (5.2) | 1.000 |
| All values are n (%)  CAT, Critical administration threshold, or patients requiring 3 or more units of PRBCs within any hour during the first six-hours  On-Target, patients with a 6-hour ratio > 0.75 and who spent >40% of their time above this threshold  Off-Target, all other patients not meeting On-Target Criteria   *a*= Patients may have more than 1 contributing cause of death  *b*= Not centrally adjudicated | | | | | | | |

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| **SUPPLEMENTAL TABLE 3.** Predicted survival using adjusted global Plasma:PRBC and Platelet:PRBC ratios | | | | | | |
|  | **Optimal**  **Ratio** | **Predicted Survival** | **Sensitivity** | **Specificity** | **Max. Youden** | **AUC** |
| **6-h Plasma:PRBC, 6-h survival** | 1.17 | 88% | 59% | 74% | 0.33 | 0.709 |
| **6-h Plasma:PRBC, 24-h survival** | 0.77 | 79% | 72% | 61% | 0.34 | 0.696 |
| **6-h Plasma:PRBC 30-d survival** | 0.81 | 73% | 67% | 70% | 0.37 | 0.732 |
|  |  |  |  |  |  |  |
| **6-h Platelet:PRBC, 6-h survival** | NA | NA | NA | NA | NA | NA |
| **6-h Platelet:PRBC, 24-h survival** | 0.75 | 81% | 60% | 70% | 0.30 | 0.672 |
| **6-h Platelet:PRBC 30-d survival** | NA | NA | NA | NA | NA | NA |
| NA, model did not converge |  |  |  |  |  |  |

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| **SUPPLEMENTAL TABLE 4.** Optimal percent time using unadjusted % Time predicted models | | | | | | | |
|  | **Ratio** | **% Time** | **Predicted Survival** | **Sensitivity** | **Specificity** | **Max. Youden** | **AUC** |
| **6-h Plasma:PRBC, 6-h survival** | 1:1 | 42 | 88% | 28% | 89% | 0.16 | 0.590 |
|  | 1.17 | 92 | 83% | 19% | 91% | 0.10 | 0.547 |
|  | 1:2 | 75 | 87% | 58% | 74% | 0.31 | 0.647 |
|  |  |  |  |  |  |  |  |
| **6-h Plasma:PRBC, 24-h survival** | 1:1 | 42 | 81% | 28% | 84% | 0.11 | 0.554 |
|  | 0.77 | 42 | 77% | 78% | 55% | 0.33 | 0.689 |
|  | 1:2 | 75 | 80% | 57% | 63% | 0.20 | 0.584 |
|  |  |  |  |  |  |  |  |
| **6-h Plasma:PRBC 30-d survival** | 1:1 | 67 | 71% | 19% | 88% | 0.07 | 0.528 |
|  | 0.81 | 58 | 70% | 34% | 76% | 0.09 | 0.530 |
|  | 1:2 | 67 | 69% | 65% | 49% | 0.14 | 0.548 |
|  |  |  |  |  |  |  |  |
| **6-h Platelet:PRBC, 6-h survival** | 1:1 | 4 | 82% | 27% | 85% | 0.13 | 0.564 |
|  | NA | NA | NA | NA | NA | NA | NA |
|  | 1:2 | 4 | 82% | 27% | 85% | 0.13 | 0.564 |
|  |  |  |  |  |  |  |  |
| **6-h Platelet:PRBC, 24-h survival** | 1:1 | 42 | 84% | 19% | 91% | 0.10 | 0.551 |
|  | 0.75 | 42 | 80% | 68% | 65% | 0.33 | 0.675 |
|  | 1:2 | 33 | 78% | 41% | 70% | 0.11 | 0.530 |
|  |  |  |  |  |  |  |  |
| **6-h Platelet:PRBC 30-d survival** | 1:1 | 42 | 70% | 18% | 87% | 0.05 | 0.517 |
|  | NA | NA | NA | NA | NA | NA | NA |
|  | 1:2 | 8 | 68% | 58% | 49% | 0.06 | 0.519 |
| NA, model did not converge |  |  |  |  |  |  |  |

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| **SUPPLEMENTAL TABLE 5.** Sensitivity Analysis for Calculating % Time over 3:4 | | | | | |
|  |  | **Optimal** | **% Time > 0.75** | |  |
| **Alternate Exposure Intervals for** | **AUC** | **% Time** | **24-h Survivors\*\*** | **24-h Deaths\*\*** | ***p*** |
| **Calculating % Time over 0.75** |  | **> 0.75** | **(n = 408)** | **(n = 116)** |  |
| Plasma:PRBC at 2-h | 0.499 | 75 | 22.5 (31.7) | 21.5 (29.2) | 0.977 |
| Platelet:PRBC at 2-h | 0.529 | 50 | 7.0 (17.2) | 9.6 (20.9) | 0.160 |
| Plasma:PRBC at 6-h or hemostasis\* | 0.599 | 72 | 46.5 (43.9) | 30.4 (37.9) | <.001 |
| Platelet:PRBC at 6-h or hemostasis\* | 0.560 | 50 | 24.2 (36.9) | 14.3 (27.6) | 0.021 |
| \*Hemostasis defined as the time of the last blood product + 1 hour or a total of 6 hours, whichever came first  \*\*Numbers are mean (SD) percent time over a ratio of 0.75 with the time interval adjusted to either 2-hour or 6-hour/hemostasis. | | | | | |