**Table S1.** List of 64 proteins identified by linear regression + causal mediation analysis in for reducing 3d-mortality, grouped by Tiers. (Related to Figure2)

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | ALL | | |  | TBI | | |  | E2-TBI | | |
|  | Protein | OR,95%Cla (Mediated Effect) | p-value | Propb |  | OR,95%Cla (Mediated Effect) | p-value | Propb |  | OR,95%Cla (Mediated Effect) | p-value | Propb |
| Tier 1 | SERPINA5 | 0.9 (0.83-0.98) | 0.01 | 108 |  | 0.86 (0.75-0.97) | 0.008 | 130 |  | 0.78 (0.64-0.94) | 0.01 | 111 |
| CHCHD7 | 0.92 (0.87-0.97) | <0.001 | 79 |  | 0.92 (0.84-0.99) | 0.024 | 65 |  | 0.83 (0.69-1.02) | 0.068 | 81 |
| APOE3 | 0.93 (0.87-0.98) | <0.001 | 70 |  | 0.92 (0.84-0.99) | 0.024 | 63 |  | 0.84 (0.69-1.03) | 0.094 | 70 |
| PLG | 0.91 (0.84-0.99) | 0.032 | 94 |  | 0.89 (0.78-1) | 0.046 | 93 |  | 0.84 (0.69-0.99) | 0.03 | 70 |
| IGFBP4 | 0.93 (0.86-0.99) | 0.012 | 69 |  | 0.92 (0.83-1) | 0.042 | 64 |  | 0.85 (0.72-0.99) | 0.022 | 62 |
| PROC | 0.92 (0.85-0.99) | 0.02 | 88 |  | 0.9 (0.81-0.97) | 0.004 | 88 |  | 0.86 (0.73-0.98) | 0.024 | 62 |
| NPS | 0.91 (0.85-0.97) | <0.001 | 92 |  | 0.9 (0.81-0.97) | 0.008 | 88 |  | 0.88 (0.75-0.99) | 0.034 | 58 |
| CPB2 | 0.93 (0.88-0.98) | 0.006 | 67 |  | 0.93 (0.85-1) | 0.038 | 54 |  | 0.88 (0.76-0.99) | 0.032 | 56 |
| F11 | 0.91 (0.85-0.97) | <0.001 | 91 |  | 0.93 (0.85-0.99) | 0.018 | 58 |  | 0.88 (0.75-1) | 0.054 | 54 |
| Tier 2 | LBP | 0.95 (0.9-1) | 0.078 | 47 |  | 0.95 (0.86-1.03) | 0.22 | 43 |  | 0.86 (0.72-0.98) | 0.016 | 67 |
| PLA2G12A | 0.98 (0.95-1.01) | 0.158 | 14 |  | 0.96 (0.88-1.01) | 0.11 | 31 |  | 0.86 (0.73-0.99) | 0.038 | 65 |
| MB | 0.99 (0.96-1.03) | 0.684 | 4 |  | 0.98 (0.92-1.02) | 0.222 | 14 |  | 0.86 (0.74-0.98) | 0.032 | 62 |
| ACAA1 | 0.99 (0.96-1.02) | 0.41 | 6 |  | 0.98 (0.92-1.03) | 0.446 | 14 |  | 0.87 (0.75-0.98) | 0.016 | 61 |
| CTSF | 0.99 (0.94-1.03) | 0.546 | 12 |  | 0.97 (0.89-1.04) | 0.382 | 29 |  | 0.89 (0.75-1.03) | 0.134 | 58 |
| C3 | 0.97 (0.9-1.04) | 0.314 | 28 |  | 0.98 (0.89-1.07) | 0.594 | 11 |  | 0.87 (0.73-1.04) | 0.118 | 56 |
| UBE2S | 1 (0.97-1.02) | 0.752 | 1 |  | 0.98 (0.93-1.02) | 0.308 | 10 |  | 0.88 (0.76-0.99) | 0.044 | 55 |
| Tier 3 | F9ab | 0.92 (0.85-0.97) | <0.001 | 90 |  | 0.91 (0.82-0.98) | 0.01 | 80 |  | 0.89 (0.76-1) | 0.054 | 49 |
| IGFALS | 0.91 (0.84-0.96) | <0.001 | 94 |  | 0.93 (0.85-1) | 0.044 | 60 |  | 0.89 (0.76-1) | 0.048 | 49 |
| PLA2G12B | 0.96 (0.92-1) | 0.046 | 34 |  | 0.95 (0.87-1) | 0.066 | 38 |  | 0.88 (0.76-1) | 0.058 | 49 |
| CLTA | 0.99 (0.95-1.01) | 0.226 | 10 |  | 0.96 (0.9-1.01) | 0.1 | 25 |  | 0.9 (0.78-1) | 0.056 | 49 |
| MMP19 | 0.95 (0.9-1) | 0.052 | 44 |  | 0.89 (0.8-0.96) | 0.004 | 88 |  | 0.89 (0.76-0.99) | 0.044 | 49 |
| APOE4 | 0.94 (0.88-0.98) | 0.002 | 63 |  | 0.94 (0.86-1) | 0.038 | 48 |  | 0.89 (0.74-1.07) | 0.176 | 48 |
| APOE2 | 0.94 (0.89-0.98) | <0.001 | 61 |  | 0.93 (0.86-0.99) | 0.038 | 52 |  | 0.89 (0.73-1.08) | 0.208 | 48 |
| HSPE1 | 1 (0.98-1.02) | 0.97 | 0 |  | 1 (0.96-1.04) | 0.892 | 0 |  | 0.9 (0.78-1) | 0.042 | 46 |
| ARL5B | 0.99 (0.96-1.01) | 0.388 | 6 |  | 0.97 (0.91-1.02) | 0.228 | 15 |  | 0.9 (0.77-1.01) | 0.078 | 46 |
| DUPD1 | 1 (0.97-1.02) | 0.914 | 1 |  | 0.99 (0.95-1.02) | 0.622 | 3 |  | 0.9 (0.78-1) | 0.046 | 46 |
| ERP29 | 0.95 (0.89-1) | 0.038 | 52 |  | 0.95 (0.87-1.01) | 0.152 | 40 |  | 0.89 (0.77-1) | 0.054 | 46 |
| F5 | 0.93 (0.87-0.98) | <0.001 | 74 |  | 0.92 (0.84-0.99) | 0.016 | 62 |  | 0.9 (0.76-1.03) | 0.114 | 45 |
| CRELD1 | 0.96 (0.89-1.02) | 0.196 | 37 |  | 0.93 (0.84-1.03) | 0.21 | 46 |  | 0.88 (0.73-1.03) | 0.128 | 45 |
| OTC | 1 (0.97-1.02) | 0.732 | 1 |  | 1.01 (0.96-1.06) | 0.728 | -1 |  | 0.9 (0.79-1) | 0.058 | 44 |
| THOP1 | 0.98 (0.95-1.01) | 0.206 | 12 |  | 0.95 (0.88-1) | 0.084 | 34 |  | 0.91 (0.79-1.01) | 0.066 | 43 |
| SHMT2 | 1 (0.99-1.03) | 0.654 | -2 |  | 0.99 (0.95-1.02) | 0.536 | 4 |  | 0.9 (0.78-1.02) | 0.086 | 42 |
| F13A1|F13B | 0.93 (0.87-0.97) | <0.001 | 77 |  | 0.91 (0.83-0.98) | 0.004 | 77 |  | 0.91 (0.78-1.03) | 0.114 | 42 |
| F9 | 0.92 (0.86-0.97) | <0.001 | 85 |  | 0.91 (0.83-0.98) | 0.012 | 73 |  | 0.9 (0.78-1.01) | 0.068 | 42 |
| MAP2K4 | 0.95 (0.88-1) | 0.056 | 56 |  | 0.92 (0.84-0.99) | 0.012 | 65 |  | 0.91 (0.79-1.01) | 0.072 | 42 |
| MRPL58 | 0.97 (0.92-1.01) | 0.146 | 33 |  | 0.95 (0.88-1) | 0.092 | 34 |  | 0.9 (0.78-1.01) | 0.066 | 42 |
| RBP4 | 0.92 (0.87-0.97) | <0.001 | 77 |  | 0.93 (0.86-0.99) | 0.024 | 50 |  | 0.9 (0.78-1.03) | 0.11 | 41 |
| SERPINF2 | 0.92 (0.84-1) | 0.052 | 76 |  | 0.9 (0.79-1.01) | 0.092 | 73 |  | 0.9 (0.75-1.04) | 0.19 | 41 |
| ITIH4 | 0.95 (0.9-0.99) | 0.024 | 51 |  | 0.93 (0.85-1) | 0.036 | 58 |  | 0.9 (0.79-1.01) | 0.062 | 41 |
| CS | 1 (0.99-1.02) | 0.92 | 0 |  | 0.99 (0.95-1.02) | 0.566 | 4 |  | 0.91 (0.79-1.01) | 0.068 | 39 |
| PCYOX1 | 0.95 (0.9-0.99) | 0.004 | 48 |  | 0.94 (0.87-1) | 0.042 | 43 |  | 0.91 (0.79-1.03) | 0.11 | 39 |
| APOA4 | 0.95 (0.9-0.99) | 0.008 | 47 |  | 0.95 (0.88-1) | 0.052 | 39 |  | 0.91 (0.79-1.01) | 0.078 | 38 |
| HLA-G | 0.96 (0.92-1) | 0.074 | 34 |  | 0.94 (0.86-1) | 0.04 | 47 |  | 0.92 (0.8-1.01) | 0.088 | 38 |
| GHRL | 1 (0.99-1.03) | 0.746 | -1 |  | 1 (0.97-1.03) | 0.964 | 1 |  | 0.91 (0.81-1.01) | 0.078 | 38 |
| GRPEL1 | 1 (0.98-1.02) | 0.996 | 0 |  | 1 (0.96-1.04) | 0.87 | 0 |  | 0.91 (0.8-1.01) | 0.08 | 38 |
| IDI2 | 1 (0.97-1.03) | 0.91 | 1 |  | 0.99 (0.94-1.03) | 0.518 | 5 |  | 0.92 (0.8-1.02) | 0.098 | 37 |
| CFP | 0.94 (0.89-0.98) | 0.004 | 59 |  | 0.94 (0.86-1) | 0.036 | 47 |  | 0.91 (0.78-1.06) | 0.176 | 37 |
| LIPG | 0.94 (0.88-0.99) | 0.02 | 58 |  | 0.94 (0.86-1.02) | 0.174 | 45 |  | 0.91 (0.8-1.01) | 0.122 | 36 |
| C5a | 0.96 (0.9-1.02) | 0.24 | 37 |  | 0.96 (0.87-1.04) | 0.334 | 34 |  | 0.92 (0.79-1.04) | 0.212 | 36 |
| C5|C6 | 0.94 (0.88-0.98) | 0.004 | 66 |  | 0.94 (0.86-1) | 0.038 | 49 |  | 0.92 (0.8-1.01) | 0.082 | 36 |
| SERPINA4 | 0.94 (0.88-0.98) | 0.004 | 63 |  | 0.93 (0.85-0.99) | 0.018 | 58 |  | 0.92 (0.8-1.03) | 0.13 | 35 |
| DYTN | 0.99 (0.96-1.02) | 0.532 | 8 |  | 0.98 (0.92-1.04) | 0.532 | 14 |  | 0.92 (0.81-1.02) | 0.124 | 35 |
| CA3 | 1 (0.98-1.03) | 0.878 | 0 |  | 0.99 (0.96-1.02) | 0.646 | 3 |  | 0.92 (0.81-1.01) | 0.08 | 35 |
| CNN1 | 1.02 (0.99-1.06) | 0.238 | -12 |  | 1 (0.96-1.05) | 0.896 | -1 |  | 0.92 (0.81-1.01) | 0.09 | 34 |
| GOT2 | 1 (0.98-1.03) | 0.772 | -1 |  | 1 (0.97-1.04) | 0.82 | 0 |  | 0.92 (0.81-1.01) | 0.08 | 34 |
| HSPA9 | 1 (0.99-1.02) | 0.814 | 0 |  | 0.99 (0.96-1.02) | 0.762 | 2 |  | 0.92 (0.81-1.01) | 0.096 | 33 |
| LPL | 0.97 (0.93-1.01) | 0.13 | 25 |  | 0.95 (0.88-1) | 0.084 | 37 |  | 0.93 (0.82-1.02) | 0.12 | 33 |
| F13B | 0.94 (0.88-0.98) | 0.002 | 62 |  | 0.93 (0.86-0.99) | 0.012 | 55 |  | 0.92 (0.81-1.03) | 0.136 | 33 |
| MDH2 | 1 (0.99-1.02) | 0.772 | -1 |  | 1 (0.98-1.03) | 0.878 | 0 |  | 0.93 (0.82-1.01) | 0.084 | 32 |
| SAA4 | 0.97 (0.93-1) | 0.08 | 25 |  | 0.97 (0.91-1.02) | 0.272 | 18 |  | 0.93 (0.81-1.03) | 0.21 | 32 |
| L3HYPDH | 1 (0.98-1.02) | 1 | 0 |  | 0.98 (0.92-1.01) | 0.216 | 15 |  | 0.93 (0.82-1.02) | 0.118 | 31 |
| C5orf38 | 0.92 (0.86-0.97) | <0.001 | 79 |  | 0.91 (0.83-0.98) | 0.012 | 68 |  | 0.92 (0.79-1.05) | 0.178 | 31 |
| CAMP | 0.98 (0.94-1) | 0.11 | 20 |  | 0.97 (0.91-1.01) | 0.23 | 19 |  | 0.93 (0.81-1.02) | 0.124 | 31 |
| C5 | 0.94 (0.89-0.99) | 0.006 | 61 |  | 0.94 (0.87-1) | 0.044 | 44 |  | 0.93 (0.82-1.02) | 0.116 | 30 |

a. Mediated effect were calculated as average causal mediation effects (ACME) defined in <https://cran.r-project.org/web/packages/mediation/vignettes/mediation.pdf>, and adjusted by age and gender.

b. Proportion of mediated effect was calculated as Mediated effect/ Total effect.

**Table S2.** Six Proteins identified by mediation analysis of prehospital TP administration for reducing 3-day mortality of E2-TBI patients. (Related to Figure 2)

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | 3d-Mortality | | |  | 30d-Mortality | | |
|  |  | OR,95%Cla (Mediated Effect) | p-value | Propb (%) |  | OR,95%Cla (Mediated Effect) | p-value | Propb (%) |
| **SERPINA5c** | ALL | 0.9 (0.83-0.98) | 0.01 | 108 |  | 0.93 (0.86-0.99) | 0.012 | 47 |
| NBI | 0.96 (0.83-1.08) | 0.52 | 39 |  | 0.96 (0.84-1.08) | 0.52 | 36 |
| E1-NBI | 1 (0.94-1.09) | 0.976 | 0 |  | 0.97 (0.87-1.07) | 0.466 | 11 |
| E2-NBI | 1.05 (0.81-1.41) | 0.72 | 4 |  | 1.05 (0.82-1.36) | 0.712 | 18 |
| TBI | 0.86 (0.75-0.97) | 0.008 | 130 |  | 0.92 (0.83-0.99) | 0.036 | 38 |
| E1-TBI | 0.98 (0.86-1.1) | 0.69 | 2 |  | 0.99 (0.89-1.06) | 0.732 | 6 |
| E2-TBI | 0.78 (0.64-0.94) | 0.01 | 111 |  | 0.94 (0.79-1.09) | 0.378 | 13 |
| **CHCHD7d** | ALL | 0.92 (0.87-0.97) | <0.001 | 79 |  | 0.95 (0.9-1) | 0.038 | 30 |
| NBI | 0.92 (0.82-1.02) | 0.122 | 59 |  | 0.93 (0.83-1.02) | 0.124 | 45 |
| E1-NBI | 0.98 (0.92-1.03) | 0.184 | 0 |  | 0.99 (0.9-1.09) | 0.892 | 1 |
| E2-NBI | 0.98 (0.8-1.18) | 0.79 | 26 |  | 0.98 (0.82-1.15) | 0.794 | 22 |
| TBI | 0.92 (0.84-0.99) | 0.024 | 65 |  | 0.98 (0.89-1.06) | 0.516 | 10 |
| E1-TBI | 0.99 (0.91-1.04) | 0.684 | 0 |  | 0.99 (0.92-1.05) | 0.756 | 1 |
| E2-TBI | 0.83 (0.69-1.02) | 0.068 | 81 |  | 1.09 (0.9-1.27) | 0.264 | -21 |
| **APOE3d** | ALL | 0.93 (0.87-0.98) | <0.001 | 70 |  | 0.96 (0.91-1) | 0.036 | 27 |
| NBI | 0.93 (0.83-1.03) | 0.208 | 48 |  | 0.94 (0.84-1.03) | 0.21 | 40 |
| E1-NBI | 0.98 (0.93-1.04) | 0.302 | 0 |  | 1 (0.91-1.08) | 0.918 | 1 |
| E2-NBI | 0.99 (0.8-1.22) | 0.908 | 15 |  | 0.99 (0.82-1.18) | 0.91 | 21 |
| TBI | 0.92 (0.84-0.99) | 0.024 | 63 |  | 0.98 (0.89-1.05) | 0.472 | 10 |
| E1-TBI | 0.99 (0.93-1.05) | 0.814 | 1 |  | 1 (0.94-1.05) | 0.906 | 1 |
| E2-TBI | 0.84 (0.69-1.03) | 0.094 | 70 |  | 1.08 (0.89-1.26) | 0.314 | -18 |
| **PLGc** | ALL | 0.91 (0.84-0.99) | 0.032 | 94 |  | 0.93 (0.86-0.99) | 0.032 | 48 |
| NBI | 0.94 (0.81-1.06) | 0.342 | 55 |  | 0.94 (0.82-1.06) | 0.342 | 43 |
| E1-NBI | 1 (0.94-1.08) | 0.86 | 0 |  | 0.99 (0.89-1.09) | 0.862 | 2 |
| E2-NBI | 1.01 (0.77-1.33) | 0.93 | 28 |  | 1.01 (0.77-1.33) | 0.932 | 38 |
| TBI | 0.89 (0.78-1) | 0.046 | 93 |  | 0.92 (0.82-1) | 0.05 | 39 |
| E1-TBI | 0.96 (0.82-1.12) | 0.64 | 3 |  | 0.97 (0.84-1.09) | 0.64 | 23 |
| E2-TBI | 0.84 (0.69-0.99) | 0.03 | 70 |  | 0.92 (0.79-1.03) | 0.136 | 19 |
| **PROCc** | ALL | 0.92 (0.85-0.99) | 0.02 | 88 |  | 0.93 (0.87-0.99) | 0.02 | 47 |
| NBI | 0.96 (0.83-1.1) | 0.566 | 48 |  | 0.96 (0.83-1.1) | 0.566 | 46 |
| E1-NBI | 0.99 (0.93-1.07) | 0.476 | 0 |  | 0.95 (0.84-1.05) | 0.272 | 20 |
| E2-NBI | 1.05 (0.8-1.41) | 0.698 | 14 |  | 1.04 (0.85-1.29) | 0.71 | 17 |
| TBI | 0.9 (0.81-0.97) | 0.004 | 88 |  | 0.94 (0.86-1) | 0.044 | 31 |
| E1-TBI | 0.94 (0.84-1.03) | 0.226 | -23 |  | 0.98 (0.9-1.05) | 0.592 | 1 |
| E2-TBI | 0.86 (0.73-0.98) | 0.024 | 62 |  | 0.92 (0.79-1.04) | 0.156 | 20 |
| **PLA2GXIIAc** | ALL | 0.98 (0.95-1.01) | 0.158 | 14 |  | 0.99 (0.95-1.01) | 0.246 | 8 |
| NBI | 1.01 (0.97-1.05) | 0.732 | 0 |  | 1.01 (0.96-1.07) | 0.648 | -2 |
| E1-NBI | 1 (0.98-1.03) | 0.98 | 0 |  | 1 (0.95-1.05) | 0.99 | 0 |
| E2-NBI | 1.08 (0.93-1.31) | 0.288 | -18 |  | 1.08 (0.93-1.3) | 0.288 | -13 |
| TBI | 0.96 (0.88-1.01) | 0.11 | 31 |  | 0.98 (0.91-1.04) | 0.404 | 9 |
| E1-TBI | 0.99 (0.92-1.07) | 0.82 | 0 |  | 0.98 (0.89-1.05) | 0.568 | 1 |
| E2-TBI | 0.86 (0.73-0.99) | 0.038 | 65 |  | 0.93 (0.82-1.02) | 0.158 | 15 |

a. Mediated effect were calculated as average causal mediation effects (ACME) defined in <https://cran.r-project.org/web/packages/mediation/vignettes/mediation.pdf>, and adjusted by age and gender.

b. Proportion of mediated effect was calculated as Mediated effect/ Total effect.

c. Common proteins between tier1\2 proteins and pure features of 3d-mortality related mediated latent factors (Z8 and Z24).

d. Common proteins between tier1\2 proteins and pure features of E2-TBI related mediated latent factors (Z16).

Abbreviations:SERPINA5: Serine protease inhibitor A5, CHCHD7: Coiled coil-helix coiled coil-helix domain 7,

APOE3: Apoprotein E3, PROC: Vit K-dependent protein C, PLG: plasminogen, PLA2GXIIA: soluble phospholipase A2 Group XII.