Slatnick: Lactate Project

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# Statistical Methods

Variables are summarized using median (interquartile range) or frequency (percentage) on the encounter level.

Receiver operating characteristic (ROC) curves were created for lactate as a predictor versus CDE within 48 hours and invasive bacterial infection within 48 hours. The area under the curve (AUC) was reported. The optimal cut-points of lactate in predicting outcomes was chosen using the maximum Youden’s index (=sensitivity+specificity-1).

**Primary outcomes:** To model potential risk factors for CDE and invasive bacterial infection within 48 hours, generalized estimating equations (GEE) with a logit link were used. An exchangeable correlation structure was used to account for correlation among patients that were seen multiple times in the ED. Univariate models were fit for each risk factor of interest. Variables that were significant in univariate models were considered for selection in a multivariable model for each outcome. Lactate (<2 vs. >=2), neutropenic status, and chemo intensity group were forced in, and the final set of predictors was selected based on the lowest Quasi-likelihood under Independence Model Criterion (QIC). Interaction terms between lactate and each predictor were tested and non-significant, so removed.

**Secondary outcomes**: Lactate group (<2 vs. >=2) was tested for association with various secondary outcomes. Time-to-death was calculated from admission to death, with censoring at 1 year for those who did not die. Kaplan-meier (KM) curves were stratified by lactate group and a Cox Proportional Hazards (Cox PH) model with a frailty term to account for correlation within an individual was used to test for significance. GEE was used to model PICU admission and viral infection (binomial) and Hospital and PICU LOS (gaussian). Hospital LOS and PICU LOS were log transformed before modeling due to non-normality, and results were back-transformed for reporting.

Analysis was done using R version 4.0.2 and the significance level was set to 0.05.

# Descriptive Results

*Section 1*

|  |  |
| --- | --- |
| Characteristic | All (n=934) |
| **Age years** | 6.6 (3.8, 12) |
| **Age\_group\_goldstein** |  |
| 3=1 month to 1 99 years | 62 (7%) |
| 4=2 years to 5 99 years | 369 (40%) |
| 5=6 years to 12 99 years | 306 (33%) |
| 6=13 to 17 99 years | 147 (16%) |
| 7= 18 years or older | 50 (5%) |
| **Sex** |  |
| female | 386 (41%) |
| male | 548 (59%) |
| **Diagnosis** |  |
| acute lymphoblastic leukemia | 432 (46%) |
| acute myeloid leukemia | 15 (2%) |
| lymphoma | 71 (8%) |
| solid tumor | 286 (31%) |
| CNS tumor | 123 (13%) |
| hematology | 4 (0%) |
| other | 3 (0%) |
| **BMT\_prior1year** |  |
| no | 860 (92%) |
| yes | 74 (8%) |
| **auto\_allo** |  |
| no BMT | 860 (92%) |
| autologous | 51 (5%) |
| allogeneic | 23 (2%) |
| **Day\_postBMT** | 108 (34.5, 184) |
| **Day\_postBMT\_miss** |  |
| missing | 859 (92%) |
| non-missing | 75 (8%) |
| **Immunosuppression BMT only** |  |
| no | 53 (71%) |
| yes | 22 (29%) |
| **Type of line** |  |
| port | 794 (85%) |
| broviac | 110 (12%) |
| picc | 12 (1%) |
| peripheral IV | 17 (2%) |
| **History of resistant or atypical organism** |  |
| no | 824 (88%) |
| yes | 110 (12%) |
| **History of clostridium difficile** |  |
| no | 841 (90%) |
| yes | 93 (10%) |

*Section 2*

|  |  |
| --- | --- |
| Characteristic | All (n=934) |
| **Lactate, initial within 8 hours** | 1.4 (1, 2) |
| <=2 | 710 (76%) |
| 2-4 | 185 (20%) |
| >4 | 39 (4%) |
| **Weight, kg** | 22 (15.1, 37.2) |
| **Weight, kg \_miss** |  |
| missing | 10 (1%) |
| non-missing | 924 (99%) |
| **maxtemp\_ED** | 38.9 (38.4, 39.4) |
| **Hypotension\_ED** |  |
| no | 830 (89%) |
| yes | 104 (11%) |
| **Initial HR** | 137 (121, 153) |
| **Initial HR\_miss** |  |
| missing | 4 (0%) |
| non-missing | 930 (100%) |
| **tachy\_goldstein** |  |
| no | 397 (43%) |
| yes | 537 (57%) |
| **Initial RR** | 25 (22, 30) |
| **Initial RR\_miss** |  |
| missing | 2 (0%) |
| non-missing | 932 (100%) |
| **tachypneic\_goldstein** |  |
| no | 112 (12%) |
| yes | 822 (88%) |
| **Initial systolic BP** | 109 (101, 117) |
| **Initial systolic BP\_miss** |  |
| missing | 5 (1%) |
| non-missing | 929 (99%) |
| **Initial diastolic BP** | 67 (59, 76) |
| **Initial diastolic BP\_miss** |  |
| missing | 5 (1%) |
| non-missing | 929 (99%) |
| **Initial SpO2** | 97 (95, 98) |
| **Chills or rigors** |  |
| no | 882 (94%) |
| yes | 52 (6%) |
| **URI symptoms** |  |
| no | 589 (63%) |
| yes | 345 (37%) |
| **Stat\_activation\_final** |  |
| no | 887 (95%) |
| yes | 47 (5%) |
| **Stat\_ini1 or Stat\_upgrade2** |  |
| no stat | 887 (95%) |
| initial | 28 (3%) |
| upgraded from sepsis yellow | 19 (2%) |

*Section 3*

|  |  |
| --- | --- |
| Characteristic | All (n=934) |
| **WBC initial** | 1.9 (0.5, 5.2) |
| **ANC initial** | 0.7 (0, 3.6) |
| **Neutropenic** |  |
| no | 502 (54%) |
| yes | 432 (46%) |
| **AMC initial** | 0.2 (0, 0.5) |
| **AMC initial\_miss** |  |
| missing | 1 (0%) |
| non-missing | 933 (100%) |
| **ALC initial** | 0.4 (0.1, 0.9) |
| **Plt…initial** | 122 (45, 222) |
| **Plt…initial\_miss** |  |
| missing | 5 (1%) |
| non-missing | 929 (99%) |
| **CRP\_within8** | 3 (1, 6.3) |
| **CRP\_within8\_miss** |  |
| missing | 897 (96%) |
| non-missing | 37 (4%) |
| **PCT\_within8** | 0.3 (0.2, 6.7) |
| **PCT\_within8\_miss** |  |
| missing | 924 (99%) |
| non-missing | 10 (1%) |
| **ESR\_within8** | 74.5 (49, 102) |
| **ESR\_within8\_miss** |  |
| missing | 930 (100%) |
| non-missing | 4 (0%) |
| **D dimer\_within8** | 1 (0.5, 2) |
| **D dimer\_within8\_miss** |  |
| missing | 869 (93%) |
| non-missing | 65 (7%) |
| **D dimer\_within8\_ISTH** |  |
| no increase (0 5 mg/mL) | 17 (28%) |
| moderate increase (0 5-3mg/mL) | 34 (57%) |
| 3=strong increase (>3mg/mL) | 9 (15%) |
| **Fibrinogen\_within8** | 370 (276.2, 445.8) |
| **Fibrinogen\_within8\_miss** |  |
| missing | 860 (92%) |
| non-missing | 74 (8%) |
| **Fibrinogen\_within8\_ISTH** |  |
| Fibrinogen>=100 | 72 (97%) |
| Fibrinogen<100 | 2 (3%) |
| **PT\_within8** | 15 (14, 15.9) |
| **PT\_within8\_miss** |  |
| missing | 845 (90%) |
| non-missing | 89 (10%) |
| **PT\_within8\_ISTH** |  |
| <=3 seconds prolonged | 76 (85%) |
| 3-6 seconds prolonged | 10 (11%) |
| 6 or more seconds prolonged | 3 (3%) |

*Section 4*

|  |  |
| --- | --- |
| Characteristic | All (n=934) |
| **New diagnosis** |  |
| no | 926 (99%) |
| yes | 6 (1%) |
| unknown | 2 (0%) |
| **Off therapy** |  |
| no | 914 (98%) |
| yes | 12 (1%) |
| unknown | 8 (1%) |
| **If so, Number of days off therapy** | 76.5 (34.8, 137) |
| **Intensity\_grade** |  |
| Least intensive | 1 (0%) |
| Moderately intensive | 272 (29%) |
| Very intensive | 551 (59%) |
| Most intensive | 101 (11%) |
| unknown | 9 (1%) |
| **Ara C ATG or Anti GD2 in the last 24 hours** |  |
| no | 900 (96%) |
| yes | 34 (4%) |
| **Antimicrobial ppx** |  |
| no | 817 (87%) |
| yes | 117 (13%) |

*Section 6*

|  |  |
| --- | --- |
| Characteristic | All (n=934) |
| **Documented infection within 48 hours** |  |
| no | 651 (70%) |
| yes | 283 (30%) |
| **Days from presentation\_infx1** | 0 (0, 1) |
| **Days from presentation\_infx1\_miss** |  |
| missing | 625 (67%) |
| non-missing | 309 (33%) |
| **First infection type** |  |
| BSI | 72 (8%) |
| GI | 46 (5%) |
| GU | 9 (1%) |
| HEENT | 12 (1%) |
| missing | 625 (67%) |
| other | 2 (0%) |
| Pneumonia | 16 (2%) |
| SSTI | 14 (1%) |
| Viral respiratory | 138 (15%) |
| **Pathogen\_Number** | 1 (1, 1) |
| **Pathogen\_Number\_miss** |  |
| missing | 625 (67%) |
| non-missing | 309 (33%) |
| **polymicrobial\_1stinfx** |  |
| 0 | 240 (78%) |
| 1 | 36 (12%) |
| 2 | 33 (11%) |
| **bacteria\_yn48hr** |  |
| no | 821 (88%) |
| yes | 113 (12%) |
| **inv\_bacteria\_yn48hr** |  |
| no | 840 (90%) |
| yes | 94 (10%) |
| **virus\_yn48hr** |  |
| no | 788 (84%) |
| yes | 146 (16%) |
| **fungus\_yn48hr** |  |
| no | 925 (99%) |
| yes | 9 (1%) |
| **parasite\_yn48hr** |  |
| no | 930 (100%) |
| yes | 4 (0%) |
| **bsi\_yn48hr** |  |
| no | 862 (92%) |
| yes | 72 (8%) |
| **pna\_yn48hr** |  |
| no | 913 (98%) |
| yes | 21 (2%) |
| **gi\_yn48hr** |  |
| no | 880 (94%) |
| yes | 54 (6%) |
| **gi\_bact\_yn48hr** |  |
| no | 900 (96%) |
| yes | 34 (4%) |
| **ssti\_yn48hr** |  |
| no | 923 (99%) |
| yes | 11 (1%) |
| **heent\_yn48hr** |  |
| no | 926 (99%) |
| yes | 8 (1%) |
| **gu\_yn48hr** |  |
| no | 922 (99%) |
| yes | 12 (1%) |
| **other\_yn48hr** |  |
| no | 933 (100%) |
| yes | 1 (0%) |

*Section 7*

|  |  |
| --- | --- |
| Characteristic | All (n=934) |
| **Admitted from ED** |  |
| no | 359 (38%) |
| yes | 575 (62%) |
| **Hospital LOS in hours includes ED for non admitted patients** | 51.1 (3.9, 116.4) |
| **Hospital LOS in hours admitted only** | 95.8 (61.7, 176.3) |
| **PICU during admission** |  |
| no | 856 (92%) |
| yes | 78 (8%) |
| **PICU admission hospital hour** | 4.4 (2.7, 6.4) |
| **PICU admission hospital hour \_miss** |  |
| missing | 856 (92%) |
| non-missing | 78 (8%) |
| **PICU within 48 hours** |  |
| no | 862 (92%) |
| yes | 72 (8%) |
| **PICU LOS hours** | 42.7 (21.5, 83.2) |
| **PICU LOS hours \_miss** |  |
| missing | 856 (92%) |
| non-missing | 78 (8%) |
| **Died within 30 days** |  |
| no | 924 (99%) |
| yes | 10 (1%) |
| **Died within 90 days** |  |
| no | 911 (98%) |
| yes | 23 (2%) |
| **Died within 1 year** |  |
| no | 862 (92%) |
| yes | 72 (8%) |
| **Died during hospital stay** |  |
| no | 926 (99%) |
| yes | 8 (1%) |
| **Day of death relative to hospital day 1** | 181.5 (65.2, 269) |
| **Day of death relative to hospital day 1\_miss** |  |
| missing | 846 (91%) |
| non-missing | 88 (9%) |
| **Vent or intubation during admission** |  |
| no | 919 (98%) |
| yes | 15 (2%) |
| **Ventilator Days** | 0 (0, 0) |
| **Ventilator Days\_miss** |  |
| missing | 631 (68%) |
| non-missing | 303 (32%) |
| **Vasopressors during admission** |  |
| no | 893 (96%) |
| yes | 41 (4%) |
| **Vaso\_duration hrs** | 24 (10.7, 41.6) |
| **Vaso\_duration hrs \_miss** |  |
| missing | 892 (96%) |
| non-missing | 42 (4%) |

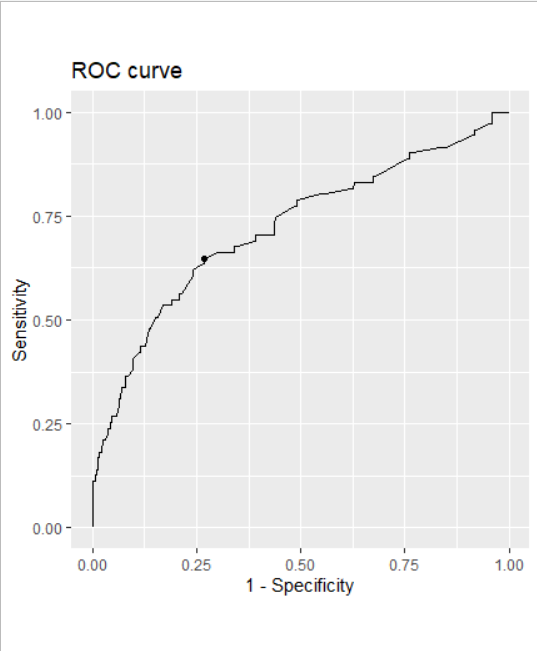
*Section 8*

|  |  |
| --- | --- |
| Characteristic | All (n=71) |
| **CDE within 48 hrs** |  |
| no | 0 (0%) |
| yes | 71 (100%) |
| **Emergent PICU transfer** |  |
| no | 59 (83%) |
| yes | 12 (17%) |
| **Respiratory insufficiency or failure** |  |
| no | 55 (77%) |
| yes | 16 (23%) |
| **60 ml kg or more in 24 hr period** |  |
| no | 16 (23%) |
| yes | 55 (77%) |
| **Vasopressors** |  |
| no | 34 (48%) |
| yes | 37 (52%) |
| **Multiple\_vaso** |  |
| no | 21 (57%) |
| yes | 16 (43%) |
| **Vaso\_duration hrs** | 18.6 (10.5, 39) |
| **Vaso\_duration hrs\_miss** |  |
| missing | 34 (48%) |
| non-missing | 37 (52%) |
| **Altered mental status** |  |
| no | 58 (82%) |
| yes | 13 (18%) |
| **Death** |  |
| no | 68 (96%) |
| yes | 3 (4%) |

# ROC Curve Results

*Cut-point of lactate for predicting CDE within 48 hours*

|  |  |  |  |
| --- | --- | --- | --- |
| OptimalCut | Sensitivity | Specificity | AUC |
| 1.86 | 0.648 | 0.732 | 0.720 |



*Cut-point of lactate for predicting invasive bacteria infection within 48 hours*

|  |  |  |  |
| --- | --- | --- | --- |
| OptimalCut | Sensitivity | Specificity | AUC |
| 1.88 | 0.489 | 0.726 | 0.623 |

# 

**Univariate model Results: CDE and invasive bacterial infection within 48 hours**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  | CDE (N=71) | | Bacterial Infection (N=94) | | n |
| Variable | Reference | OR (95% CI) | pval | OR (95% CI) | pval |  |
| Age, years | - | 1.12 (1.07, 1.17) | <0.001 | 1.01 (0.97, 1.05) | 0.6775 | 934 |
| Diagnosis | ALL/AML |  | 0.6655 |  | 0.3074 | 934 |
| CNS Tumor |  | 0.73 (0.29, 1.86) |  | 0.97 (0.49, 1.96) |  |  |
| Lymphoma |  | 1.6 (0.7, 3.67) |  | 1.19 (0.56, 2.55) |  |  |
| Other |  | 2.06 (0.23, 18.49) |  | 3.28 (0.78, 13.86) |  |  |
| Solid Tumor |  | 1.01 (0.56, 1.81) |  | 0.72 (0.41, 1.27) |  |  |
| Lactate, continuous | - | 1.87 (1.59, 2.18) | <0.001 | 1.35 (1.13, 1.61) | <0.001 | 934 |
| Lactate, categorical | <=2 |  | <0.001 |  | <0.001 | 934 |
| Lactate 2-4 |  | 3.41 (2.03, 5.72) |  | 1.79 (1.09, 2.94) |  |  |
| Lactate >4 |  | 12.63 (6.3, 25.34) |  | 4.88 (2.35, 10.14) |  |  |
| Lactate categorical, >2 | <=2 | 4.65 (2.97, 7.28) | <0.001 | 2.24 (1.46, 3.44) | <0.001 | 934 |
| Lactate cutpoint, CDE: >=1.86 | <1.86 | 4.87 (3.07, 7.72) | <0.001 |  |  | 934 |
| Lactate cutpoint, bact: >=1.88 | <1.88 |  |  | 2.52 (1.65, 3.83) | <0.001 | 934 |
| maxtemp\_ED | - | 1.02 (0.98, 1.07) | 0.2778 | 1.04 (0.97, 1.12) | 0.2846 | 934 |
| Hypotension\_ED: yes | no | 36.13 (19.9, 65.5) | <0.001 | 4.84 (2.97, 7.88) | <0.001 | 934 |
| tachy\_goldstein: yes | no | 3.39 (1.91, 6.02) | <0.001 | 1.84 (1.14, 2.96) | 0.0119 | 934 |
| tachypneic\_goldstein: yes | no | 1.77 (0.72, 4.35) | 0.214 | 1.3 (0.67, 2.52) | 0.4415 | 934 |
| Chills or rigors: yes | no | 2.82 (1.33, 5.94) | 0.0066 | 2.48 (1.23, 4.98) | 0.0111 | 934 |
| URI symptoms: yes | no | 0.66 (0.39, 1.11) | 0.1177 | 0.8 (0.5, 1.28) | 0.3496 | 934 |
| Stat\_activation\_final: yes | no | 39.88 (19.42, 81.88) | <0.001 | 6.6 (3.66, 11.89) | <0.001 | 934 |
| WBC, initial | - | 0.98 (0.92, 1.05) | 0.5749 | 0.99 (0.95, 1.04) | 0.6952 | 934 |
| ANC, initial | - | 0.99 (0.92, 1.07) | 0.8256 | 1.01 (0.94, 1.08) | 0.8359 | 934 |
| Neutropenic, yes | no | 1.6 (0.98, 2.6) | 0.0594 | 1.83 (1.16, 2.9) | 0.0101 | 934 |
| AMC, initial | - | 0.56 (0.28, 1.1) | 0.0921 | 0.66 (0.29, 1.48) | 0.3116 | 933 |
| ALC, initial | - | 0.79 (0.58, 1.08) | 0.1348 | 0.83 (0.6, 1.15) | 0.2564 | 934 |
| Plt, initial | - | 1 (0.99, 1) | 0.0313 | 1 (0.99, 1) | 0.0074 | 929 |
| Hemoglobin, initial | - | 0.96 (0.84, 1.1) | 0.5642 | 0.87 (0.77, 0.97) | 0.0108 | 931 |
| D dimer\_within8 | - | 1.44 (1.1, 1.89) | 0.0087 | did not converge | - | 65 |
| Fibrinogen\_within8 | - | 1 (0.99, 1) | 0.1561 | did not converge | - | 74 |
| PT\_within8 | - | 1.66 (1.31, 2.12) | <0.001 | 1.74 (1.30, 2.35) | <0.001 | 89 |
| Intensity Group | Least/Moderate |  | 0.0434 |  | 0.0171 | 925 |
| Very intensive |  | 0.99 (0.54, 1.84) |  | 1 (0.59, 1.7) |  |  |
| Most intensive |  | 2.25 (1.06, 4.77) |  | 2.39 (1.16, 4.93) |  |  |

Blue = force into multivariable model, Green = consider in multivariable model

**Multivariable model Results: CDE and invasive bacterial infection within 48 hours**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | **CDE** | | **Bacterial Infection** | |
| **Variable** | **Ref** | **OR (95% CI)** | **pval** | **OR (95% CI)** | **pval** |
| Lactate >2 | <=2 | 4.4 (2.21, 8.74) | <0.001 | 1.93 (1.21, 3.07) | 0.0057 |
| Neutropenic, yes | no | 1.03 (0.52, 2.05) | 0.9318 | 1.68 (1.03, 2.74) | 0.0366 |
| Intensity Group | Least/Moderate |  |  |  |  |
| Very intensive |  | 0.61 (0.26, 1.46) | 0.2697 | 0.9 (0.52, 1.54) | 0.6906 |
| Most intensive |  | 2.4 (0.87, 6.6) | 0.0893 | 2.24 (1.07, 4.69) | 0.0331 |
| Age, years | - | 1.06 (1, 1.13) | 0.0484 | - | - |
| Hypotension ED, yes | no | 14.79 (7.15, 30.61) | <0.001 | 2.32 (1.25, 4.33) | 0.0081 |
| Tachy\_goldstein, yes | no | 2.16 (0.99, 4.73) | 0.0534 |  |  |
| Stat activation, yes | no | 10.15 (3.81, 27.06) | <0.001 | 3.03 (1.48, 6.21) | 0.0024 |
| Chills or rigors, yes | no | - | - | 2 (0.95, 4.24) | 0.0687 |

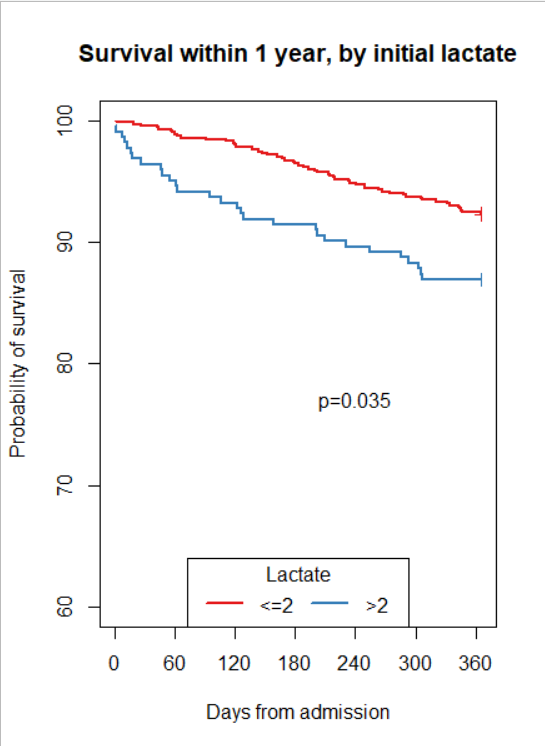
Interpretation:

After adjusting for neutropenia, intensity group, age, hypotension, tachy goldstein, and stat activation, having a lactate above 2 was significantly associated with an elevated risk of CDE within 48 hours (p<0.001). Other factors independently associated with CDE included older age, hypotension in ED, and stat activation.

After adjusting for neutropenia, intensity group, hypotension, stat activation, and chills/rigors, having a lactate above 2 was significantly associated with an elevated risk of an invasive bacterial infection within 48 hours (p=0.0057). Other factors independently associated with invasive bacterial infection within 48 hours included being in the most intensive group (compared to least/moderate groups), being neutropenic, having hypotension in the ED, and a stat activation.

# Secondary outcomes

**Outcome: 1-year survival**



|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variable | ref | Hazard ratio | pval | nobs |
| Lactate >2 | <=2 | 1.79 95% CI: (1.04, 13.07) | 0.0352 | 925 |

**Outcome: PICU admission**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variable | ref | Odds ratio | pval | nobs |
| Lactate >2 | <=2 | 3.46 95% CI: (2.21, 5.40) | <0.001 | 925 |

**Outcome: PICU LOS**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variable | ref | Estimate | pval | nobs |
| Lactate >2 | <=2 | 0.92 95% CI: (0.56, 1.5) | 0.7275 | 76 |

**Outcome: Hospital LOS, admitted patients only**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Var | ref | Estimate | pval | nobs |
| Lactate >2 | <=2 | 1.23 95% CI: (1.04, 1.44) | 0.0135 | 562 |

**Outcome: Viral infection**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Var | ref | OR | pval | nobs |
| Lactate >2 | <=2 | 1.12 95% CI: (0.78, 1.63) | 0.5341 | 925 |