***Supplementary Digital Content***

**Evaluation of repeated qSOFA measurements among patients with suspected infection**

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**Appendix**

(a) *Defining a cohort with suspected infection*

We identified digital evidence that the clinical team suspected infection using the first combination of a body fluid culture order (e.g., blood, urine, cerebrospinal fluid, etc.) and at least one dose of antibiotics (oral or parenteral) within a specified time frame (1). When body fluid culture sampling occurred first, the antibiotic must have been ordered within 72 hours. When antibiotic administration occurred first, culture sampling must have been ordered with 24 hours. We excluded cases that received only a single dose of a prophylactic antibiotic in the operating room. We defined the “time zero” for suspected infection as the occurrence of the first culture or antibiotic event.

(b) *Generating the cohort for heat map analysis*

We included all deaths in the analysis (N=1,769). A total of 28.4% of encounters had an initial qSOFA of 0 (n=503), 40.6% had an initial qSOFA of 1 (n=719), 26.5% had an initial qSOFA of 2 (n=468), and 4.5% had an initial qSOFA of 3 (n=79). For a comparision group of survivors, we randomly selected a subset of equal number to that of total deaths (N=1,769). In this subset, a total of 68.3% of encounters had an initial qSOFA of 0 (n=1209), 25.8% had an initial qSOFA of 1 (n=457), 5.7% had an initial qSOFA of 2 (n=101), and 0.1% had an initial qSOFA of 3 (n=2).

(c) *Group-based trajectory modeling methods*

Group-based trajectory modeling (GBTM), an adaptation of finite mixture modeling, is used widely for data with repeated measures in a variety of clinical conditions (2-4). GBTM groups represent latent clusters of encounters following similar trajectories of qSOFA. For this analysis, we assumed: i.) an underlying zero-inflated Poisson distribution, ii.) trajectories could be modeled as polynomials over time, and iii.) the presence of between three to five latent groups. We varied the number of potential groups and polynomial values during model building, and we determined the best-fitting GBTM by minimizing the Bayesian Information Criterion (BIC). The BIC is a quantity that uses a likelihood-based stepwise approach that can be used for model selection by retaining variables that improve a model’s overall ability to predict the outcome of interest while incorporating a penalty for too many variables. We performed GBTM on data after multiple imputations.

(d) *Discussion of multiple imputations procedure*

Missing qSOFA data was common in our database (**eTable 1**). In our sensitivity analysis, we assumed that missing data was related to the observed covariates, and was classified as “missing at random.” We used a flexible multivariable imputation procedure of multiple chained regression equations (multiple imputation by chained equations, i.e., MICE) which generated values for all missing data using the observed data for all patients (5). We included all covariates and our primary outcome in the imputation procedure. We modeled variables using ordinal regression. MICE may still lead to bias in the setting of missingness > 50%, but this bias is generally less than that resulting from complete case analysis (which assumes missing completely at random) (6). The imputation procedure created five independent datasets.

(e) *Analysis after multiple imputations*

We assessed the AUROC for the primary outcome (hospital mortality) in the independent imputed datasets. We report the median (range) of these measures across our imputed validation sets for three reasons: 1) the normality assumption of these statistics is uncertain, 2) they are generally bounded by 0 and 1, and 3) they are unlikely to have a symmetric distribution (6).

(f) *Sensitivity analyses*

First, to understand changes in predictive validity over a range of baseline risk, we divided the cohort into deciles of risk predicted by the baseline model. We then determined the AUROC for initial and repeated measurements of qSOFA within each decile of baseline risk. Second, we restricted to encounters with suspected infection that began in the ED and repeated analyses. Third, to account for potential confounding by limitations of life-sustaining therapy, we assessed performance when this variable was included in our baseline model. Fourth, we restricted to complete cases and repeated analyses. Fifth, we used a flexible multivariable procedure of MICE to generate values for all missing data using the observed data among eligible encounters (7). We determined the odds ratios (with 95% CI) from the baseline model, and baseline model with qSOFA measures using Rubin’s rules (8). We report the mean AUROC (range) for various models across the imputed data sets. GBTM results are presented only on the imputed datasets.

**eFigure 1.** Patient accrual



*Abbreviations*: ED – emergency department, ICU – intensive care unit, ICU encounters – in ICU at time of suspected infection, N – no. of encounters, Non-ICU encounters – outside the ICU at time of suspected infection, PACU – post-anesthesia care unit, qSOFA – quick Sepsis-related Organ Function Assessment

**eFigure 2.** Area under the receiver operating characteristic curve for in-hospital mortality of repeated qSOFA measurements across deciles of baseline risk among all encounters (N=37,591)

*Abbreviations*: AUROC – area under the receiver operating characteristic curve, GBTM – group-based trajectory modeling, qSOFA – quick Sepsis-related Organ Function Assessment

The x-axis divides the cohort into deciles of baseline risk, determined by age, sex, race, and comorbidities. Solid grey lines indicate the AUROC of baseline model within each decile. Colored point estimates and error bars show the AUROC with 95% CI of repeated qSOFA measurements added to the baseline model within a decile.

**eFigure 3.** Area under the receiver operating characteristic curve of repeated qSOFA measurements versus baseline risk model among complete cases (N=14,076; *Panel A*) and restricting to those that began outside the ICU (N=10,085; *Panel B*)



*Abbreviations*: AUROC – area under the receiver operating characteristic curve, ICU – intensive care unit, qSOFA – quick Sepsis-related Organ Function Assessment

**eTable 1.** Summary measures of qSOFA missingness

|  |  |  |  |
| --- | --- | --- | --- |
| Variables | All patients | Survivors | Deaths |
| Total patients, no. | 37,591 | 35,822 | 1,769 |
| Initial qSOFA only, no. (%) | 1,576 (4) | 1,529 (4) | 47 (3) |
| Total epochs with qSOFA measurement out of 8, no. (%) |  |  |  |
|   | 1 to 2 | 2,292 (6) | 2,208 (6) | 84 (5) |
|   | 3 to 4 | 3,181 (8) | 3,080 (9) | 101 (6) |
|   | 5 to 6 | 11,095 (30) | 10,836 (30) | 259 (15) |
|   | 7 to 8 | 21,023 (56) | 19,698 (55) | 1,325 (75) |
| All qSOFA measurements present, no. (%) | 14,076 (37) | 12,978 (36) | 1,098 (62) |
| Discharged prior to 48 hours, no. (%) | 3,387 (9) | 3,238 (9) | 149 (8) |
| *Abbreviations:* qSOFA - quick Sepsis-related Organ Function Assessment |

**eTable 2.** Patient characteristics among those missing initial qSOFA (N=10,728)

|  |  |  |  |
| --- | --- | --- | --- |
| Variable | All patients | Survivors | Deaths |
| Total patients, no. | 10,728 | 10,646 | 82 |
| Age, years, mean (SD) | 52.8 (21.8) | 52.6 (21.8) | 69.5 (16.0) |
| Male gender, no. (%) | 3,653 (34) | 3,610 (34) | 43 (52) |
| Race or ethnicity, no. (%) |  |  |  |
|   | White | 7,835 (73) | 7,766 (73) | 69 (84) |
|   | Black | 1,895 (18) | 1,887 (18) | 8 (10) |
|   | Other | 998 (9) | 993 (9) | 5 (6) |
| Weighted Charlson sum, mean (SD) | 0.7 (1.3) | 0.7 (1.3) | 1.5 (2.1) |
| Surgery prior to infection suspected, no. (%) | 692 (7) | 683 (6) | 9 (11) |
| Onset of infection within 48 hours of admission, no. (%) | 9,713 (91) | 9,650 (91) | 63 (77) |
| Unit location at the time infection suspected, no. (%) |  |  |  |
|   | ED | 6,681 (62) | 6,672 (63) | 9 (11) |
|   | Ward | 3,283 (31) | 3,229 (30) | 54 (66) |
|   | ICU | 9 (0) | 6 (0) | 3 (4) |
|   | PACU or Procedure unit | 54 (1) | 54 (1) | 0 (0) |
|   | Stepdown unit | 684 (6) | 668 (6) | 16 (20) |
|   | Other or missing | 17 (0) | 17 (0) | 0 (0) |
| SIRS day of infection suspected, mean (SD) | 0.9 (0.9) | 0.9 (0.9) | 1.4 (1.1) |
|   | median [IQR] | 1 [0, 1] | 1 [0, 1] | 1 [0, 2] |
| SOFA score day of infection suspected, mean (SD) | 0.8 (1.4) | 0.8 (1.3) | 2.7 (2.9) |
|   | median [IQR] | 0 [0, 1] | 0 [0, 1] | 2 [0, 4] |
| Serum lactate measured on day of infection suspected, no. (%) | 234 (2) | 224 (2) | 10 (12) |
| Serum lactate ≥2.0 mmol/L, no. (%) if measured  | 86 (1) | 78 (1) | 8 (10) |
| Limitation of life-sustaining therapies at time infection suspected, no. (%)a | 142 (1) | 130 (1) | 12 (15) |
| Outcomes |  |  |  |
|  | ICU admission, no. (%) | 526 (5) | 468 (4) | 58 (71) |
|  | Hospital length of stay, median [IQR] days | 2 [1, 6] | 2 [1, 6] | 12 [6, 19] |
| aLimitation of life-sustaining therapy defined as do-not-resuscitate, do-not-intubate, or comfort care order in place at time of suspected infection*Abbreviations:* ED – emergency department, ICU – intensive care unit, IQR – interquartile range, PACU – post-anesthesia care unit, SD – standard deviation, SIRS – systemic inflammatory response syndrome, SOFA – Sequential Organ Failure Assessment. |

**eTable 3.** Baseline and repeated measures of qSOFA among survivors and deaths (N=37,591)

|  |  |  |  |
| --- | --- | --- | --- |
|   | All patients(N=37,591) | Survivors(N=35,822) | Deaths(N=1,769) |
| Initial qSOFA, mean (SD) | 0.4 (0.6) | 0.4 (0.6) | 1.1 (0.9) |
| *Summary qSOFA measurements* |
|  | Maximum at 24 hours, mean (SD) | 0.7 (0.7) | 0.6 (0.7) | 1.5 (0.9) |
|  | Maximum at 48 hours, mean (SD) | 0.8 (0.8) | 0.7 (0.7) | 1.7 (0.8) |
|  | Mean across 48 hours, mean (SD) | 0.4 (0.5) | 0.3 (0.4) | 1.1 (0.7) |
| *Crude trajectory groups, no. (%)* |
|  | I.) Initial qSOFA 0, maximum qSOFA <2 | 24,136 (64) | 23,781 (66) | 355 (20) |
|  | II.) Initlal qSOFA 0, maximum qSOFA ≥2 | 1,201 (3) | 1,053 (3) | 148 (8) |
|  | III.) Initial qSOFA 1, maximum qSOFA <2 | 7,307 (19) | 6,982 (19) | 325 (18) |
|  | IV.) Initial qSOFA 1, maximum qSOFA ≥2 | 2,494 (7) | 2,100 (6) | 394 (22) |
|  | V.) Initial qSOFA ≥2, maximum qSOFA <2 | 528 (1) | 471 (1) | 57 (3) |
|  | VI.) Initial qSOFA ≥2, maximum qSOFA ≥2 | 1,925 (5) | 1,435 (4) | 490 (28) |
| *qSOFA group by GBTM, no. (%)*a |
|   | Low | 13.317 (35) | 13,198 (37) | 119 (7) |
|   | Increasing | 3,208 (9) | 3,137 (9) | 71 (4) |
|   | Decreasing | 10,921 (29) | 10,698 (30) | 214 (12) |
|   | Moderate | 7,301 (19) | 6,727 (19) | 574 (33) |
|   | High | 2,853 (8) | 2,062 (6) | 791 (45) |
| aDetermined in data after multiple imputation; illustrative proportions derived from single imputeddataset*Abbreviations:* GBTM – group-based trajectory modeling, qSOFA – quick Sepsis-related Organ Function Assessment, SD – standard deviation. |

**eTable 4.** Odds ratios for baseline multivariable logistic regression model and after adjustment for repeated measures of qSOFA among all encounters (N=37,591)

|  |  |  |  |
| --- | --- | --- | --- |
| Baseline model variablesa | Odds ratio (95% CI) forin-hospital mortality[N=37,591] | Odds ratio (95% CI) forin-hospital mortalityoutside the ICU [N=32,865] | Odds ratio (95% CI) for in-hospital mortality for encounters in the ED [N=16,265] |
| Age, yrs | 1.02 (1.02-1.03) | 1.02 (1.02-1.03) | 1.03 (1.03-1.04) |
| Male gender | 1.40 (1.27-1.54) | 1.29 (1.14-1.46) | 1.23 (1.04-1.46) |
| Race |  |  |  |
|   | White  | *ref* | *ref* | *ref* |
|   | Black | 1.05 (0.90-1.23) | 1.17 (0.97-1.42) | 1.29 (1.02-1.63) |
|   | Other | 1.11 (0.95-1.29) | 0.71 (0.55-0.91) | 0.51 (0.33-0.77) |
| Weighted Charlson co-morbidity score | 1.12 (1.09-1.15) | 1.16 (1.12-1.20) | 1.17 (1.12-1.23) |
| **qSOFA variable added to baseline model**b |  |  |  |
|   | Initial qSOFA | 3.58 (3.37-3.80) | 3.07 (2.81-3.34) | 3.58 (3.22-3.99) |
|   | Maximum qSOFA at 24 hours | 3.91 (3.67-4.16) | 3.45 (3.18-3.75) | 4.10 (3.68-4.57) |
|   | Maximum qSOFA at 48 hours | 4.42 (4.15-4.71) | 4.12 (3.79-4.48) | 4.59 (4.12-4.57) |
|   | Mean qSOFA across 48 hours | 8.55 (7.91-9.24) | 8.46 (7.62-9.39) | 9.09 (7.96-10.38) |
| **Crude trajectory groups added to baseline model**c |  |  |  |
|   | I.) Initial qSOFA 0, maximum qSOFA <2 | *ref* | *ref* | *ref* |
|   | II.) Initlal qSOFA 0, maximum qSOFA ≥2 | 8.76 (7.14-10.74) | 8.45 (6.69-10.68) | 11.70 (8.23-16.64) |
|   | III.) Initial qSOFA 1, maximum qSOFA <2 | 3.09 (2.65-3.61) | 2.55 (2.14-3.03) | 3.80 (2.95-4.90) |
|   | IV.) Initial qSOFA 1, maximum qSOFA ≥2 | 12.10 (10.40-14.09) | 11.53 (9.57-13.88) | 15.67 (12.06-20.36) |
|  | V.) Initial qSOFA ≥2, maximum qSOFA <2 | 7.61 (5.65-10.24) | 4.58 (2.91-7.22) | 7.30 (4.27-12.49) |
|  | VI.) Initial qSOFA ≥2, maximum qSOFA ≥2 | 23.16 (19.96-26.88) | 16.41 (13.27-20.29) | 22.96 (17.54-30.05) |
| aBaseline model uses linear age and weighted Charlson co-morbidity score. The two models that include repeated measures of qSOFA use multivariable fractional polynomials for age and weighted Charlson score.bEach variable added to the baseline model individually.cThe crude trajectory groups added as a single categorical variable to the baseline model.*Abbreviations:* qSOFA – quick Sepsis-related Organ Function Assessment |

**eTable 5.** Area under the receiver operating characteristic curve for in-hospital mortality in the baseline multivariable logistic regression model and repeated qSOFA variables (N=37,591)

|  |  |  |  |
| --- | --- | --- | --- |
| **Model** | **AUROC (95% CI) for in-hospital mortality [N=37,591]** | **AUROC (95% CI) for in-hospital mortality among encounters outside the ICU [N=32,865]** | **AUROC (95%CI) for in-hospital mortality for encounters in the ED [N=16,265]** |
| Basel model alone | 0.63 (0.62-0.65) | 0.67 (0.65-0.68) | 0.69 (0.67-0.71) |
| *qSOFA variable added to baseline model*a |  |  |  |
|  | Initial qSOFA at 24 hours | 0.79 (0.78-0.80) | 0.76 (0.74-0.77) | 0.80 (0.79-0.82) |
|  | Maximum qSOFA at 24 hours | 0.81 (0.80-0.82) | 0.79 (0.78-0.80) | 0.84 (0.82-0.85) |
|  | Maximum qSOFA at 48 hours | 0.83 (0.82-0.84) | 0.82 (0.81-0.83) | 0.85 (0.86-0.89) |
|  | Mean qSOFA across 48 hours | 0.86 (0.85-0.86) | 0.84 (0.82-0.85) | 0.87 (0.86-0.89) |
| *Crude trajectory groups added to the baseline model*b | 0.83 (0.82-0.83) | 0.80 (0.79-0.82) | 0.84 (0.83-0.86) |
| aEach variable added to the baseline model individually.bThe crude trajectory groups added as a single categorical variable to the baseline model.*Abbreviations:* AUROC – area under the receiver operating characteristic curve, GBTM – group-based trajectory modeling, qSOFA – quick Sepsis-related Organ Function Assessment |

**eTable 6.** Odds ratios for baseline multivariable logistic regression model and after adjustment for repeated measures of qSOFA in multiply-imputed data (N=37,591)

|  |  |  |
| --- | --- | --- |
| Baseline model variablesa | Odds ratio (95% CI) forin-hospital mortality [N=37,591] | Odds ratio (95% CI) forin-hospital mortality outside the ICU [N=32,865] |
| Age, years | 1.02 (1.02-1.03) | 1.03 (1.02-1.03) |
| Male gender | 1.40 (1.27-1.54) | 1.29 (1.14-1.46) |
| Race |  |  |
|   | White  | *ref* | *ref* |
|   | Black | 1.05 (0.90-1.23) | 1.17 (0.97-1.42) |
|   | Other | 1.11 (0.95-1.30) | 0.71 (0.55-0.91) |
| Weighted Charlson co-morbidity score | 1.12 (1.09-1.15) | 1.16 (1.13-1.20) |
| **qSOFA variable added to baseline model**b |
|   | Initial qSOFA | 3.58 (3.37-3.80) | 3.07 (2.81-3.34) |
|   | Maximum qSOFA at 24 hours | 4.03 (3.77-4.30) | 3.52 (3.22-3.84) |
|   | Maximum qSOFA at 48 hours | 4.70 (4.39-5.03) | 4.30 (3.93-4.70) |
|   | Mean qSOFA across 48 hours | 8.64 (7.99-9.34) | 8.74 (7.85-9.73) |
| **Crude trajectory groups added to baseline model**c |
|   | I.) Initial qSOFA 0, maximum qSOFA <2 | *ref* | *ref* |
|   | II.) Initlal qSOFA 0, maximum qSOFA ≥2 | 7.56 (6.17-9.26) | 7.11 (5.65-8.94) |
|   | III.) Initial qSOFA 1, maximum qSOFA <2 | 2.88 (2.45-3.38) | 2.40 (1.99-2.88) |
|   | IV.) Initial qSOFA 1, maximum qSOFA ≥2 | 12.48 (10.72-14.52) | 11.63 (9.65-14.01) |
|  | V.) Initial qSOFA ≥2, maximum qSOFA <2 | 5.73 (4.03-8.16) | 3.19 (1.73-5.88) |
|  | VI.) Initial qSOFA ≥2, maximum qSOFA ≥2 | 24.01 (20.67-27.89) | 17.17 (13.89-21.24) |
| **GBTM qSOFA groups added to the baseline model**d |
|  | Low | *ref* | *ref* |
|  | Increasing | 3.05 (1.27-7.33) | 3.14 (1.16-8.47) |
|  | Decreasing | 2.24 (1.67-3.02) | 2.07 (1.47-2.91) |
|  | Intermediate | 8.96 (6.76-11.88) | 7.72 (5.68-10.50) |
|  | High | 42.29 (30.68-58.30) | 37.39 (26.69-52.38) |
| aBaseline model uses linear age and weighted Charlson co-morbidity score. All other models use multivariable fractional polynomials for age and weighted Charlson score.bEach variable added to the baseline model individually.cThe crude trajectory groups added as a single categorical variable to the baseline model.dGBTM qSOFA groups added as a single categorical variable to the baseline model.*Abbreviations:* GBTM – group-based trajectory modeling, qSOFA – quick Sepsis-related Organ Function Assessment |

**eTable 7.** Area under the receiver operating characteristic curve for in-hospital mortality in the baseline multivariable logistic regression model and qSOFA variables in multiply-imputed data (N=37,591)

|  |  |  |
| --- | --- | --- |
| Model | Mean AUROC (range) for in-hospital mortality [N=37,591] | Mean AUROC (range) forin-hospital mortality outside the ICU [N=32,865] |
| Baseline model alone | 0.63 (0.63-0.63) | 0.67 (0.67-0.67) |
| *qSOFA variable added to baseline model*a |  |  |
|   | Initial qSOFA | 0.79 (0.79-0.79) | 0.76 (0.76-0.76) |
|   | Maximum qSOFA at 24 hours | 0.81 (0.81-0.81) | 0.79 (0.79-0.79) |
|   | Maximum qSOFA at 48 hours | 0.83 (0.83-0.83) | 0.81 (0.81-0.81) |
|   | Mean qSOFA across 48 hours | 0.86 (0.86-0.86) | 0.84 (0.84-0.84) |
| *Crude trajectory groups added to the baseline model*b | 0.83 (0.83-0.83) | 0.80 (0.80-0.81) |
| *GBTM qSOFA groups added to the baseline model*c | 0.85 (0.84-0.85) | 0.83 (0.83-0.83) |
| aEach variable added to the baseline model individually.bThe crude trajectory groups added as a single categorical variable to the baseline model.cGBTM qSOFA groups added as a single categorical variable to the baseline model.*Abbreviations:* AUROC – area under the receiver operating characteristic curve, GBTM – group-based trajectory modeling, qSOFA – quick Sepsis-related Organ Function Assessment |

**eTable 8.** Patient characteristics among encounters that began in the ED (N=16,265)

|  |  |  |  |
| --- | --- | --- | --- |
| Variable | All patients | Survivors | Deaths |
| Total patients, no. | 16,265 | 15,677 | 588 |
| Age, years, mean (SD) | 62.3 (19.4) | 61.9 (19.4) | 72.3 (14.7) |
| Male gender, no. (%) | 6,843 (42) | 6,567 (42) | 276 (47) |
| Race or ethnicity, no. (%) |  |  |  |
|   | White | 12,325 (76) | 11,855 (76) | 470 (80) |
|   | Black | 2,484 (15) | 2,389 (15) | 95 (16) |
|   | Other | 1,456 (9) | 1,433 (9) | 23 (4) |
| Weighted Charlson sum, mean (SD) | 1.2 (1.6) | 1.1 (1.5) | 1.8 (2.1) |
| Surgery prior to infection suspected, no. (%) | 1,887 (12) | 1,821 (12) | 66 (11) |
| SIRS day of infection suspected, mean (SD) | 1.2 (1.1) | 1.2 (1.0) | 2.0 (1.2) |
|   | median [IQR] | 1 [0, 2] | 1 [0, 2] | 2 [1, 3] |
| SOFA score day of infection suspected, mean (SD) | 1.3 (2.1) | 1.2 (1.9) | 4.2 (4.2) |
|   | median [IQR] | 1 [0, 2] | 1 [0, 2] | 3 [1, 7] |
| Serum lactate measured on day of infection suspected, no. (%) | 1,938 (12) | 1,659 (11) | 279 (47) |
| Serum lactate ≥2.0 mmol/L, no. (%) if measured  | 804 (5) | 603 (4) | 201 (34) |
| Limitation of life-sustaining therapies at time infection suspected, no. (%)a | 103 (1) | 93 (1) | 10 (2) |
| Outcomes |  |  |  |
|  | ICU admission, no. (%) | 3,206 (20) | 2,721 (17) | 485 (82) |
|  | Hospital length of stay, median [IQR] days | 5 [3, 8] | 5 [3, 8] | 7 [4, 13] |
| aLimitation of life-sustaining therapy defined as do-not-resuscitate, do-not-intubate, or comfort care order in place at time of suspected infection*Abbreviations:* ED – emergency department, ICU – intensive care unit, IQR – interquartile range, PACU – post-anesthesia care unit, SD – standard deviation, SIRS – systemic inflammatory response syndrome, SOFA – Sequential Organ Failure Assessment. |

**eTable 9.** Odds ratios for baseline multivariable logistic regression model including limitations of life-sustaining therapy and repeated measures of qSOFA among all encounters (N=37,591)

|  |  |  |
| --- | --- | --- |
| Baseline model variablesa | Odds ratio (95% CI) forin-hospital mortality[N=37,591] | Odds ratio (95% CI) forin-hospital mortalityoutside the ICU [N=32,865] |
| Age, yrs | 1.02 (1.02-1.02) | 1.02 (1.02-1.03) |
| Male gender | 1.41 (1.28-1.55) | 1.30 (1.14-1.47) |
| Race |  |  |
|   | White  | *ref* | *ref* |
|   | Black | 1.06 (0.91-1.24) | 1.19 (0.98-1.44) |
|   | Other | 1.12 (0.96-1.30) | 0.71 (0.56-0.91) |
| Weighted Charlson co-morbidity score | 1.12 (1.09-1.15) | 1.16 (1.12-1.19) |
| Limitation of life-sustaining therapies at time infection suspectedb | 1.46 (1.15-1.85) | 1.63 (1.24-2.16) |
| **qSOFA variable added to baseline model**c |
|   | Initial qSOFA | 3.58 (3.37-3.81) | 3.07 (2.82-3.35) |
|   | Maximum qSOFA at 24 hours | 3.91 (3.67-4.16) | 3.46 (3.18-3.76) |
|   | Maximum qSOFA at 48 hours | 4.43 (4.15-4.72) | 4.14 (3.80-4.50) |
|   | Mean qSOFA across 48 hours | 8.57 (7.93-9.26) | 8.49 (7.64-9.42) |
| **Crude trajectory groups added to baseline model**d |
|   | I.) Initial qSOFA 0, maximum qSOFA <2 | *ref* | *ref* |
|   | II.) Initlal qSOFA 0, maximum qSOFA ≥2 | 8.74 (7.12-10.72) | 8.42 (6.66-10.64) |
|   | III.) Initial qSOFA 1, maximum qSOFA <2 | 3.09 (2.65-3.60) | 2.55 (2.14-3.03) |
|   | IV.) Initial qSOFA 1, maximum qSOFA ≥2 | 12.14 (10.43-14.12) | 11.60 (9.63-13.98) |
|  | V.) Initial qSOFA ≥2, maximum qSOFA <2 | 7.57 (5.62-10.20) | 4.56 (2.89-7.20) |
|  | VI.) Initial qSOFA ≥2, maximum qSOFA ≥2 | 23.26 (20.04-26.99) | 16.56 (13.39-20.50) |
| aBaseline model uses linear age and weighted Charlson co-morbidity score. The models that include repeated measures of qSOFA use multivariable fractional polynomials for age and weighted Charlson score.bLimitation of life-sustaining therapy defined as do-not-resuscitate, do-not-intubate, or comfort care order in place at time of suspected infectioncEach variable added to the baseline model individually.dThe crude trajectory groups added as a single categorical variable to the baseline model.*Abbreviations:* qSOFA – quick Sepsis-related Organ Function Assessment |

**eTable 10.** Area under the receiver operating characteristic curve for in-hospital mortality in a regression model including limitations of life-sustaining therapy and repeated qSOFA variables (N=37,591)

|  |  |  |
| --- | --- | --- |
| Model | AUROC (95% CI) for in-hospital mortality [N=37,591] | AUROC (95% CI) forin-hospital mortality outside the ICU [N=32,865] |
| Baseline model including limitation on life-sustaining therapy at the time of infectiona | 0.64 (0.62-0.65) | 0.67 (0.65-0.69) |
| *qSOFA variable added to baseline model*b |  |  |
|   | Initial qSOFA | 0.79 (0.78-0.80) | 0.76 (0.75-0.77) |
|   | Maximum qSOFA at 24 hours | 0.81 (0.80-0.82) | 0.79 (0.78-0.80) |
|   | Maximum qSOFA at 48 hours | 0.82 (0.82-0.84) | 0.82 (0.81-0.83) |
|   | Mean qSOFA across 48 hours | 0.86 (0.85-0.86) | 0.84 (0.82-0.85) |
| *Crude trajectory groups added to the baseline model*c | 0.83 (0.82-0.84) | 0.81 (0.79-0.82) |
| aLimitation of life-sustaining therapy defined as do-not-resuscitate, do-not-intubate, or comfort care order in place at time of suspected infectionbEach variable added to the baseline model individually.cThe crude trajectory groups added as a single categorical variable to the baseline model.*Abbreviations:* AUROC – area under the receiver operating characteristic curve, qSOFA – quick Sepsis-related Organ Function Assessment |

**eTable 11.** Odds ratios for baseline multivariable logistic regression model and repeated measures of qSOFA among complete cases (N=14,076)

|  |  |  |
| --- | --- | --- |
| Baseline model variablesa | Odds ratio (95% CI) forin-hospital mortality [N=14,076] | Odds ratio (95% CI) forin-hospital mortality outside the ICU [N=10,085] |
| Age, years | 1.02 (1.02-1.02) | 1.03 (1.02-1.03) |
| Male gender | 1.28 (1.13-1.45) | 1.28 (1.07-1.52) |
| Race |  |  |
|   | White  | *ref* | *ref* |
|   | Black | 1.29 (1.05-1.58) | 1.54 (1.18-2.02) |
|   | Other | 1.02 (0.85-1.23) | 0.69 (0.50-0.95) |
| Weighted Charlson co-morbidity score | 1.02 (0.98-1.05) | 1.05 (1.00-1.10) |
| **qSOFA variable added to baseline model**b |
|   | Initial qSOFA | 2.50 (1.06-1.37) | 2.15 (1.92-2.41) |
|   | Maximum qSOFA at 24 hours | 2.81 (2.59-3.05) | 2.47 (2.21-2.76) |
|   | Maximum qSOFA at 48 hours | 3.25 (2.98-3.54) | 3.00 (2.66-3.37) |
|   | Mean qSOFA across 48 hours | 5.39 (4.87-5.97) | 5.01 (4.36-5.76) |
| **Crude trajectory groups added to baseline model**c |
|   | I.) Initial qSOFA 0, maximum qSOFA <2 | *ref* | *ref* |
|   | II.) Initlal qSOFA 0, maximum qSOFA ≥2 | 5.66 (4.33-7.40) | 5.37 (3.92-7.36) |
|   | III.) Initial qSOFA 1, maximum qSOFA <2 | 2.58 (2.06-3.24) | 2.14 (1.63-2.80) |
|   | IV.) Initial qSOFA 1, maximum qSOFA ≥2 | 6.82 (5.54-8.40) | 6.27 (4.86-8.10) |
|  | V.) Initial qSOFA ≥2, maximum qSOFA <2 | 3.87 (2.55-5.89) | 2.25 (1.12-4.54) |
|  | IV.) Initial qSOFA ≥2, maximum qSOFA ≥2 | 11.72 (9.55-14.38) | 8.04 (6.08-10.63) |
| aBaseline model uses linear age and weighted Charlson co-morbidity score. The models that include repeated measures of qSOFA use multivariable fractional polynomials for age and weighted Charlson score.bEach variable added to the baseline model individually.cThe crude trajectory groups added as a single categorical variable to the baseline model.*Abbreviations:* qSOFA – quick Sepsis-related Organ Function Assessment. |

**References**

1. Seymour CW, Liu VX, Iwashyna TJ, et al.: Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016; 315:762–774

2. Nagin DS, Odgers CL: Group-based trajectory modeling in clinical research. *Annu Rev Clin Psychol* 2010; 6:109–138

3. Lo-Ciganic W-H, Gellad WF, Huskamp HA, et al.: Who Were the Early Adopters of Dabigatran?: An Application of Group-based Trajectory Models. *Med Care* 2016; 54:725–732

4. Ferrante LE, Pisani MA, Murphy TE, et al.: Functional trajectories among older persons before and after critical illness. *JAMA Intern Med* 2015; 175:523–529

5. van Buuren S, Boshuizen HC, Knook DL: Multiple imputation of missing blood pressure covariates in survival analysis. *Stat Med* 1999; 18:681–694

6. Marshall A, Altman DG, Royston P, et al.: Comparison of techniques for handling missing covariate data within prognostic modelling studies: a simulation study. *BMC Med Res Methodol* 2010; 10:7

7. Royston P: Multiple imputation of missing values. *Stata Journal* 2004; 4:227–241

8. Rubin DB: Multiple Imputation for Nonresponse in Surveys. Hoboken, NJ: John Wiley & Sons; 2004.