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Supplementary appendix

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Supplement to: Wright SW, Hantrakun V, Rudd KE, et al. Enhanced bedside mortality prediction combining point-of-care lactate and the quick Sequential Organ Failure Assessment (qSOFA) score in patients hospitalised with suspected infection in southeast Asia: a cohort study. *Lancet Glob Health* 2022; **10:** e1281–88.

Enhanced bedside mortality prediction combining point-of-care lactate and the quick Sequential Organ Failure Assessment (qSOFA) score in patients hospitalized with suspected infection in southeast Asia.

Supplementary information

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Supplementary Table 1: Patient characteristics by survival status at 28-days

Characteristics	Derivation cohort (N=4980)		External validation cohort (N=792)	
	Survivors (N=4164)	Non-survivors (N=816)	Survivors (N=690)	Non-survivors (N=102)
Demographics				
Age, median (IQR)	56 (39-70)	66 (52-78)	49 (32-63)	62 (50-76)
Female sex, N (%)	1981 (48)	344 (42)	310 (45)	33 (32)
Pre-existing conditions				
Charlson Comorbidity Index, median (IQR)	2 (0-3)	3 (1-4)	1 (0-3)	2 (1-4)
Diabetes, N (%)	793 (19)	213 (26)	99 (14)	23 (23)
Chronic liver disease, N (%)	93 (2)	39 (5)	9 (1)	5 (5)
Chronic kidney disease, N (%)	403 (10)	142 (17)	38 (6)	11 (11)
Chronic cardiovascular disease, N (%)	228 (6)	54 (7)	35 (5)	8 (8)
Chronic lung disease, N (%)	293 (7)	99 (12)	27 (4)	8 (8)
Cancer, N (%)	57 (1)	25 (3)	6 (0.9)	3 (3)
HIV, N (%)	56 (1)	6 (1)	2 (0·3)	0 (0)
Transferred from another facility, N (%)	3062 (74)	746 (91)	446 (65)	55 (54)
Admission characteristics				
Symptom duration, median days (IQR)	3 (1-4)	3 (1-4)	3 (2-5)	3 (2-5)
Mechanical ventilation, N (%)	455 (11)	346 (42)	38 (6)	29 (28)
Vasoactive medications, N (%)	976 (23)	299 (37)	113 (16)	50 (49)

Supplementary Table 2: Availability of variables at enrollment

Variable, total available (%)	Derivation cohort (N=4980)	External validation cohort (N=792)
Outcome at 28 days	4980 (100)	792 (100)
Point-of-care lactate	4980 (100)	792 (100)
Baseline risk factors		
Sex	4980 (100)	792 (100)
Age	4980 (100)	792 (100)
Pre-existing condition data	4980 (100)	792 (100)
Transfer status	4980 (100)	792 (100)
qSOFA		
Systolic blood pressure	4979 (99·9)	792 (100)
Respiratory rate	4970 (99·8)	787 (99·4)
Mental status assessment	4980 (100)	514 (65)
modified SOFA		
Mechanical ventilation	4980 (100)	792 (100)
Platelet count	4952 (99)	790 (99·8)
Total bilirubin	3642 (73)	368 (46)
Mean arterial blood pressure	4979 (99·9)	791 (99·9)
Vasoactive medications	4980 (100)	792 (100)
Mental status assessment	4980 (100)	514 (65)
Creatinine	4890 (98)	761 (96)

Supplementary Table 3: Clinical severity of illness by cohort

A. Derivation cohort

Severity of illness variable	Cohort (n=4980)	Survivors (n=4164)	Non-survivors (n=816)	p value[a]
Modified SOFA score, median (IQR)	4 (2-6)	3 (1-5)	7 (4-10)	<0·0001
Modified SOFA score ≥2, N (%)	3799 (76)	3023 (73)	776 (95)	<0·0001
qSOFA score, median (IQR)	2 (1-2)	2 (1-2)	2 (2-3)	<0·0001
qSOFA score ≥2, N (%)	2953 (59)	2298 (55)	655 (80)	<0·0001
Lactate (mmol/L), median (IQR)	1·8 (1·2-2·8)	1·7 (1·2-2·3)	3·4 (2·1-7·1)	<0·0001
Lactate <2·0 mmol/L, N (%)	2854 (57)	2678 (64)	176 (22)	-
Lactate ≥2·0 & <4·0 mmol/L, N (%)	1394 (28)	1114 (27)	280 (34)	<0·0001
Lactate ≥4·0 mmol/L, N (%)	732 (15)	372 (9)	360 (44)	-

[a] p value represents comparison of variables or group of variables (lactate groups) between survivors and non-survivors

B. External validation cohort

Severity of illness variable	Cohort (n=792)	Survivors (n=690)	Non-survivors (n=102)	p value[a]
Modified SOFA score, median (IQR)	2 (0-4)	2 (0-4)	5 (3-9)	<0.0001
Modified SOFA score ≥2, N (%)	443 (56)	351 (51)	92 (90)	<0·0001
qSOFA score, median (IQR)	1 (0-2)	1 (0-2)	2 (1-2)	<0·0001
qSOFA score ≥2, N (%)	282 (36)	222 (32)	60 (59)	<0·0001
Lactate (mmol/L), median (IQR)	2·0 (1·5-2·9)	1·9 (1·4-2·5)	4·5 (2·2-7·6)	<0·0001
Lactate <2·0 mmol/L, N (%)	384 (49)	362 (52)	22 (22)	-
Lactate ≥2·0 & <4·0 mmol/L, N (%)	287 (36)	261 (38)	26 (26)	<0·0001
Lactate ≥4·0 mmol/L, N (%)	121 (15)	67 (10)	54 (53)	-

[a] p value represents comparison of variables or group of variables (lactate groups) between survivors and non-survivors

Supplementary Table 4: Mortality by qSOFA score, lactate concentration and qSOFA-lactate score

A. Derivation cohort: Percentage of patients who died by 28-days (N/total)

	Lactate (mmol/L)		
qSOFA	**<2**	**2-<4**	**≥4**
0	1% (5/366)	15% (11/72)	41% (7/17)
1	5% (51/1073)	14% (54/401)	34% (33/98)
2	8% (98/1301)	20% (154/790)	43% (182/428)
3	19% (22/114)	47% (61/131)	73% (138/189)

B. External validation cohort: Percentage of patients who died by 28-days (N/total)

	Lactate (mmol/L)		
qSOFA	**<2**	**2-<4**	**≥4**
0	2% (2/119)	5% (4/81)	29% (4/14)
1	5% (7/155)	11% (12/106)	37% (13/35)
2	9% (9/100)	7% (6/83)	45% (21/47)
3	40% (4/10)	24% (4/17)	64% (16/25)

qSOFA-lactate score of 5

qSOFA-lactate score of 4

qSOFA-lactate score of 3

qSOFA-lactate score of 2

qSOFA-lactate score of 1

qSOFA-lactate score of 0

Supplementary Table 5: qSOFA and lactate to predict 28-day mortality in the derivation cohort

Model	Variable	28-day mortality[a]	Crude OR	95% CI	p value	LR[b]	IDI[c]
qSOFA	**qSOFA**						
	0	23/455	1·0		<0·0001	ref	ref
	1	138/1572	1·8	1·2-2·9			
	2	434/2519	3·9	2·5-6·0			
	3	221/434	19·5	12·3-30·9			
qSOFA + binary lactate score[d]	**qSOFA**						
	0	23/455	1·0		<0·0001	<0·0001	0·07 ± 0·004, P<0·0001
	1	138/1572	1·4	0·9-2·3			
	2	434/2519	2·5	1·6-3·9			
	3	221/434	9·9	6·1-15·9			
	Lactate						
	<2·0	176/2854	1·0		<0·0001		
	≥2·0	640/2126	5·1	4·2-6·1			
qSOFA + ternary lactate score[e]	**qSOFA**						
	0	23/455	1·0		<0·0001	<0·0001	0·11 ± 0·006, P<0·0001
	1	138/1572	1·5	0·9-2·4			
	2	434/2519	2·3	1·5-3·6			
	3	221/434	7·9	4·9-12·7			
	Lactate						
	<2·0	176/2854	1·0		<0·0001		
	≥2·0 & <4·0	280/1394	3·3	2·7-4·1			
	≥4·0	360/732	10·2	8·2-12·7			

[a] 28-day mortality represents number of deaths at 28 days/total number of patients for each variable.
[b] p values derived from likelihood ratio tests comparing the models of qSOFA + lactate score to the model of qSOFA alone
[c] IDI: Integrated discrimination improvement; values represent model improvement estimates for models of qSOFA and lactate over a model of qSOFA alone ± standard error
[d] Binary lactate score: 0 points for lactate <2·0 mmol/L, 1 point for lactate ≥2·0 mmol/L
[e] Ternary lactate score: 0 points for lactate <2·0 mmol/L, 1 point for lactate ≥2·0 & <4·0 mmol/L and 2 points for lactate ≥4·0 mmol/L

Supplementary Table 6: Predictive models for mortality by transfer status in the derivation cohort

A. Derivation cohort

Transfer	Model	AUC	95% CI	Δ AUC, qSOFA	p value[a]
No (N=1172)	qSOFA	0·73	0·67-0·79	-	ref
	Lactate score[b]	0·85	0·79-0·90	0·12	0·0013
	qSOFA-lactate score[c]	0·86	0·82-0·91	0·13	<0·0001
	Modified SOFA	0·87	0·83-0·92	0·14	<0·0001
Yes (N=3808)	qSOFA	0·64	0·62-0·66	-	ref
	Lactate score[b]	0·73	0·71-0·75	0·09	<0·0001
	qSOFA-lactate score[c]	0·74	0·72-0·76	0·10	<0·0001
	Modified SOFA	0·72	0·70-0·74	0·08	<0·0001

[a] p value of model compared to qSOFA model of same transfer status
[b] Lactate score is a 0-2 score composed of 0 points for lactate <2·0 mmol/L, 1 point for lactate ≥2·0 & <4·0 mmol/L and 2 points for lactate ≥4·0 mmol/L
[c] qSOFA-lactate score is a 0-5 point score composed of the 3-point qSOFA score + 0 points for lactate <2·0 mmol/L, 1 point for lactate ≥2·0 & <4·0 mmol/L and 2 points for lactate ≥4·0 mmol/L

B. External validation cohort

Transfer	Model	AUC	95% CI	Δ AUC, qSOFA	p value[a]
No (N=291)	qSOFA	0·69	0·61-0.77	-	ref
	Lactate score[b]	0·76	0·68-0·84	0·07	0·22
	qSOFA-lactate score[c]	0·80	0·73-0·87	0·11	0.0005
	Modified SOFA	0·70	0·62-0.78	0·01	0·84
Yes (N=501)	qSOFA	0·67	0·60-0.75	-	ref
	Lactate score[b]	0·72	0·64-0·80	0·05	0·40
	qSOFA-lactate score[c]	0·77	0·71-0·83	0·10	0·0007
	Modified SOFA	0·83	0·78-0·89	0·16	0·0002

[a] p value of model compared to qSOFA model of same transfer status
[b] Lactate score is a 0-2 score composed of 0 points for lactate <2·0 mmol/L, 1 point for lactate ≥2·0 & <4·0 mmol/L and 2 points for lactate ≥4·0 mmol/L
[c] qSOFA-lactate score is a 0-5 point score composed of the 3-point qSOFA score + 0 points for lactate <2·0 mmol/L, 1 point for lactate ≥2·0 & <4·0 mmol/L and 2 points for lactate ≥4·0 mmol/L

Supplementary Table 7: Discrimination of qSOFA, lactate score, qSOFA-lactate and modified SOFA added to baseline risk for 28-day mortality

A. Derivation cohort

Model	AUC (95% CI)	Δ AUC, Baseline	p value[b]	Δ AUC, qSOFA	p value[b]	Δ AUC, qSOFA-lactate	p value[b]
Baseline risk[a]	0·69 (0·67-0·71)	-	-	-0·06	<0·0001	-0·12	<0·0001
Baseline + qSOFA	0·75 (0·73-0·76)	0·06	<0·0001	-	-	-0·06	<0·0001
Baseline + lactate score	0·81 (0·79-0·82)	0·12	<0·0001	0·06	<0·0001	0	0·54
Baseline + qSOFA-lactate	0·81 (0·80-0·83)	0·12	<0·0001	0·06	<0·0001	-	-
Baseline + modified SOFA	0·80 (0·78-0·82)	0·11	<0·0001	0·05	<0·0001	-0·01	0·089

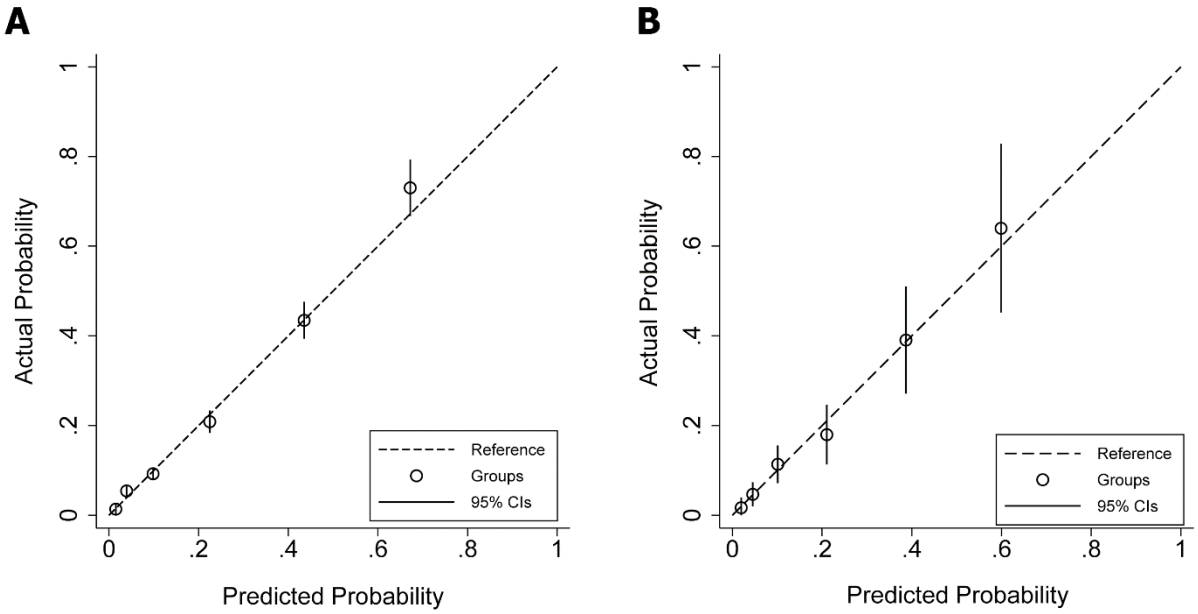
[a] Baseline risk determined based on age, sex, Charlson Comorbidity Index and transfer status.
[b] p value < 0·01 considered significant due to multiple comparison adjustment.

B. External validation cohort

Model	AUC (95% CI)	Δ AUC, Baseline	p value[b]	Δ AUC, qSOFA	p value[b]	Δ AUC, qSOFA-lactate	p value[b]
Baseline risk[a]	0·71 (0·66-0·76)	-	-	-0·06	0·0084	-0·12	<0·0001
Baseline + qSOFA	0·77 (0·72-0·81)	0·06	0·0084	-	-	-0·06	<0·0001
Baseline + lactate score	0·81 (0·77-0·86)	0·10	0·0001	0·04	0·10	-0·02	0·15
Baseline + qSOFA-lactate	0·83 (0·80-0·87)	0·12	<0·0001	0·06	<0·0001	-	-
Baseline + modified SOFA	0·81 (0·77-0·85)	0·10	<0·0001	0·04	0·067	-0·02	0·26

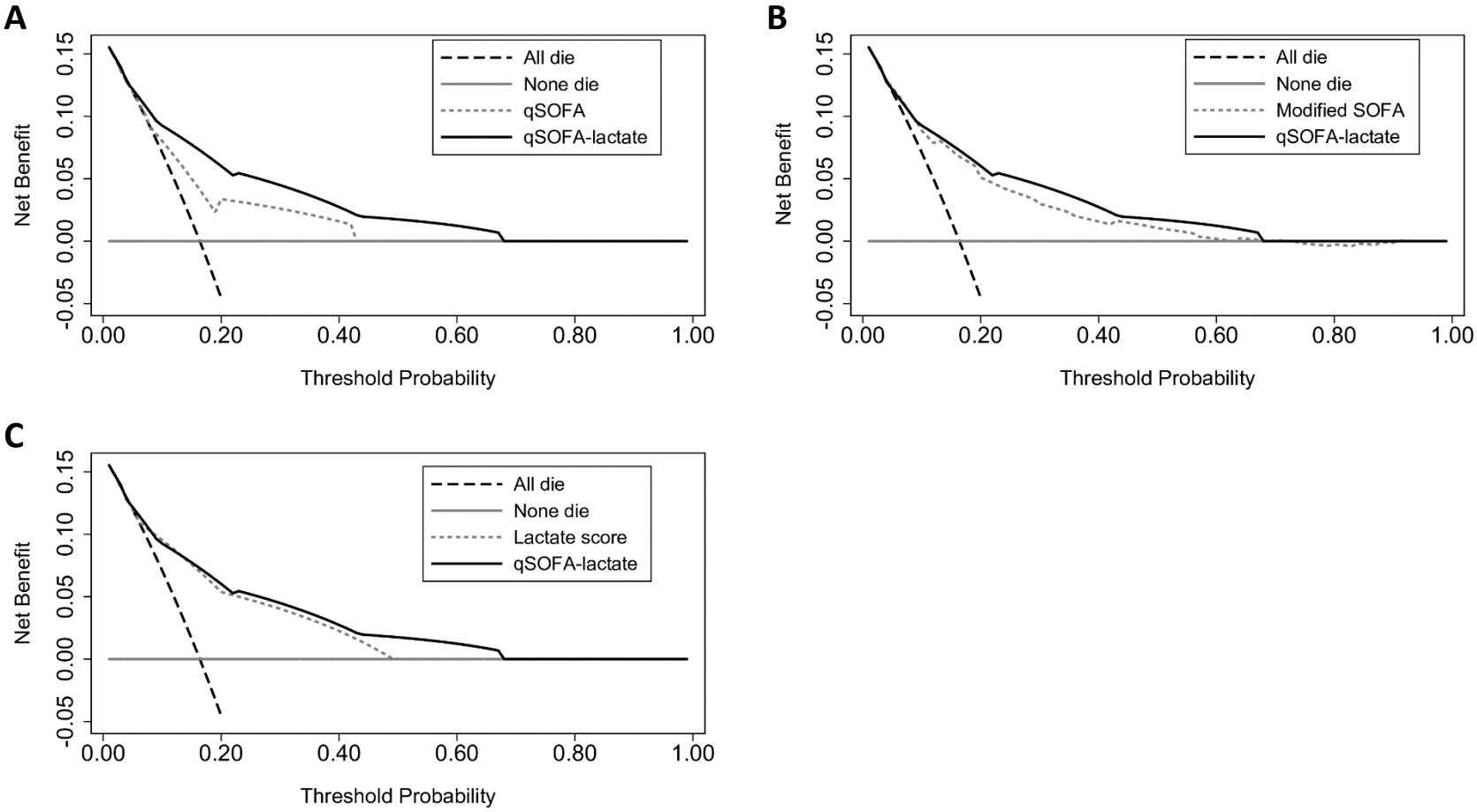
[a] Baseline risk determined based on age, sex, Charlson Comorbidity Index and transfer status.
[b] p value < 0·01 considered significant due to multiple comparison adjustment.

Supplementary Figure 1: Model calibration plots of qSOFA-lactate score model



Supplementary Figure 1: Model calibration plots of qSOFA-lactate score model. Calibration plots of actual (observed) 28-day mortality and predicted 28-day mortality based on each 0-5 score (circles) of the qSOFA-lactate score in the derivation (A) and external validation (B) cohorts. Vertical lines represent 95% confidence intervals, and the dashed line represents perfect correlation between actual and predicted outcomes.

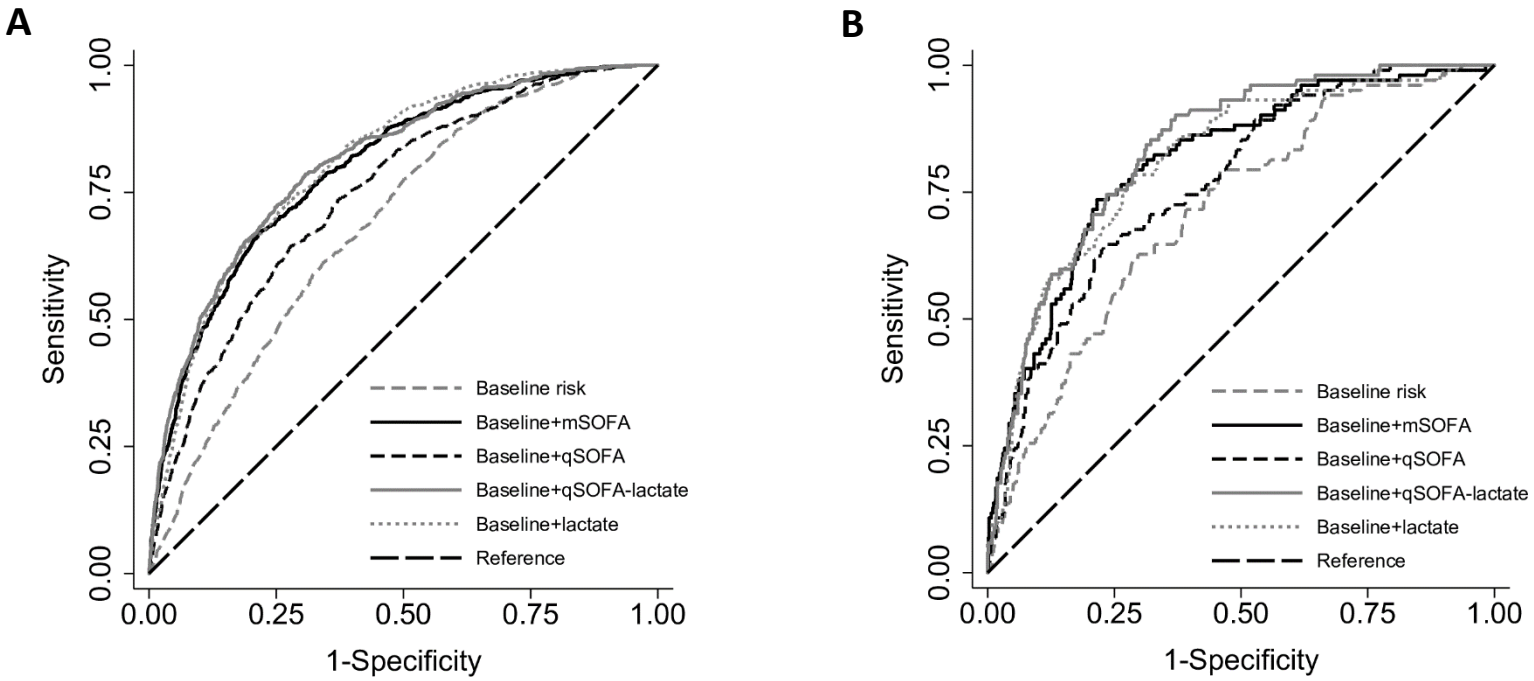
Supplementary Figure 2. Net benefit of a qSOFA-lactate score compared to qSOFA, a modified SOFA score and a lactate score in the derivation cohort



Supplementary Figure 2: Net benefit of a qSOFA-lactate score compared to qSOFA, a modified SOFA score and a lactate score in the derivation cohort. The graphs represent the net benefit of the qSOFA-lactate score compared to either the qSOFA score (A), the modified SOFA score (B) or the ternary lactate score (C). The dashed black line represents the assumption that all patients will die within 28 days. The solid gray line represents the assumption that no patients will die within 28 days. The net benefit is derived from the following equation: ((true-positive count/N)-(false-positive count/N)*(threshold probability/1-threshold probability)). Threshold probability, on the x-axis, is where the expected benefit of using the prediction model is equal to the expected benefit of not using the

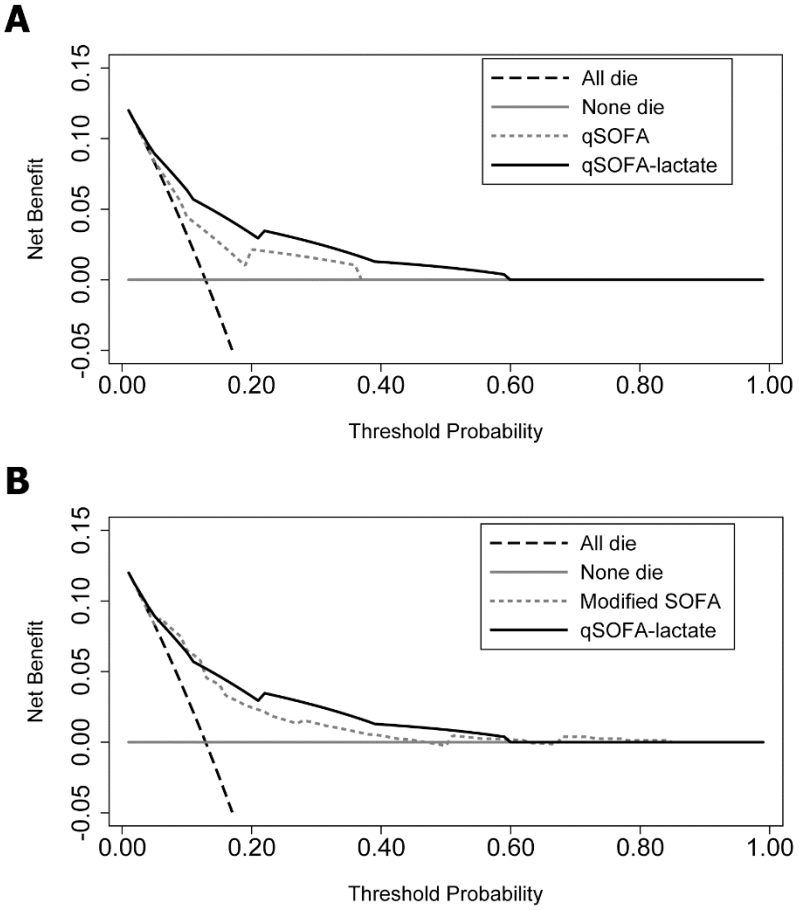
prediction model. The threshold probability and predicted probability are independent, and the threshold probability can vary by patient or healthcare provider. At the threshold probability of 0, assuming all patients die ("All die") yields a net benefit of 0·16 (the mortality of the derivation cohort). The net benefit of 0·16 would be equivalent to identifying 16 patients per 100 patients, all of whom died. Assuming no patients will die ("None die") gives a net benefit of 0 for the entire range of threshold probabilities. "All die" crosses with "None die" at the threshold probability of 0·16 (the mortality of the derivation cohort) and continues to a negative net benefit at higher threshold probabilities. For each score, the predicted mortality of the model was used in net benefit estimations.

Supplementary Figure 3: Receiver operating curve for modified SOFA, qSOFA, qSOFA-lactate score and lactate score added to baseline risk for 28-day mortality



Supplementary Figure 3: Receiver operating curve for modified SOFA, qSOFA, qSOFA-lactate score and lactate score added to baseline risk for 28-day mortality. Area under the receiver operating curves (AUC) for a baseline risk model including age, sex, Charlson Comorbidity Index and transfer status and the baseline risk model plus either modified SOFA (mSOFA), qSOFA, qSOFA-lactate or ternary lactate score model for 28-day mortality discrimination in the derivation (A) and external validation (B) cohorts.

Supplementary Figure 4. Net benefit of a qSOFA-lactate score compared to qSOFA and a modified SOFA score in the external validation cohort



Supplementary Figure 4: Net benefit of a qSOFA-lactate score compared to qSOFA and a modified SOFA score in the external validation cohort. The graphs represent the net benefit of the qSOFA-lactate score compared to either the qSOFA score (A) or the modified SOFA score (B). The dashed black line represents the assumption that all patients will die in 28 days. The solid gray line represents the assumption that no patients will die in 28 days. The net benefit is derived from the following equation: ((true-positive count/N)-(false-positive count/N)*(threshold probability/1-threshold probability)). Threshold probability (on the x-axis) is where the expected benefit of using the prediction model is equal to the expected benefit of not using the prediction model. The threshold probability and predicted probability are independent, and the threshold probability can vary by patient or healthcare provider. At the threshold probability of 0, assuming all patients die

("All die") yields a net benefit of 0·13 (the mortality of the derivation cohort). The net benefit of 0·13 would be equivalent to identifying 13 patients per 100 patients, all of whom died. Assuming no patients will die ("None die") gives a net benefit of 0 for the entire range of threshold probabilities. "All die" crosses with "None die" at the threshold probability of 0·13 (the mortality of the derivation cohort) and continues to a negative net benefit at higher threshold probabilities. For each score, the predicted mortality of the model was used in net benefit estimations.

Supplementary Methods 1. Clinical score definitions

A modified SOFA score was calculated for all subjects at the time of enrollment in the Ubon-sepsis and SEAICRN cohorts. Modifications were necessary given the absence of some data points such as inotrope and vasopressor doses and partial pressure of oxygen in arterial blood (PaO_2). Therefore, in the cardiovascular component of the SOFA score, 2/4 points were given for only dobutamine or dopamine infusions and 3/4 points were given for epinephrine or norepinephrine infusions. For the respiratory component of the SOFA score, 2/4 points were given if advanced respiratory support (endotracheal tube or mechanical ventilation) was utilized but arterial blood gas results were not available. These modifications have been reported previously.[1,2] In the Ubon-sepsis cohort, a Glasgow Coma Scale (GCS) calculated by the study team at enrollment was used in the modified SOFA calculation. In the SEAICRN cohort, a GCS was used for the modified SOFA calculation when present in the medical record. If no GCS was recorded in the medical record but altered mental status was noted on study inclusion, 1 point was given for the neurological modified SOFA component.

For qSOFA score calculation, 1 point was given for altered mental status for a GCS<15 for both cohorts or, in the SEAICRN cohort, for altered mental status at study inclusion if no GCS was documented in the medical record.

To be consistent with the approach taken in the development of the original qSOFA score as well as several follow-up studies, where individual components of the qSOFA or the modified SOFA score were not available, they were assumed to be normal and zero points were given.[3–5]

Supplementary References

1 Hantrakun V, Somayaji R, Teparrukkul P, *et al*. Clinical epidemiology and outcomes of community acquired infection and sepsis among hospitalized patients in a resource limited setting in Northeast Thailand: A prospective observational study (Ubon-sepsis). *PLoS One* 2018; **13**: 1–14.

2 Wright SW, Lovelace-Macon L, Hantrakun V, *et al*. sTREM-1 predicts mortality in hospitalized patients with infection in a tropical, middle-income country. *BMC Med* 2020; **18**: 1–9.

3 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 - J Am Med Assoc* 2016; **315**: 762–74.

4 Raith EP, Udy AA, Bailey M, *et al*. Prognostic accuracy of the SOFA score, SIRS criteria, and qSOFA score for in-hospital mortality among adults with suspected infection admitted to the intensive care unit. *JAMA - J Am Med Assoc* 2017; **317**: 290–300.

5 Rudd KE, Seymour CW, Aluisio AR, *et al*. Association of the quick sequential (sepsis-related) organ failure assessment (qSOFA) score with excess hospital mortality in adults with suspected infection in low- and middle-income countries. *JAMA - J Am Med Assoc* 2018; **319**: 2202–11.