EVMS EM Journal Club: Clinical Prediction/Decision Rule

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Objectives: "To evaluate the validity of clinical criteria to identify patients with suspected infection who are at risk of sepsis."

Methods:

- Retrospective cohort study
- Age ≥18 years
- All suspected infection between 2010-2012 at 12 community and academic hospitals in the UPMC healthcare system (derivation and initial validation group split 50/50)
- Validated in 20 Kaisep Permanente, 130 US VA's, 1 city EMS agency, 1 German hospital
- Suspected infection defined as: antibiotic given first and culture sample obtained within 24 hours or if culture sampling first, antibiotics ordered within 72 hours
- Random 50/50 split sample of derivation cohort and validation cohort
- SIRS, SOFA, modified LODS calculated for the time window from 48 hours before to 24 hours after onset of infection

GUIDE	COMMENTS
I. Is this a newly derived prediction rule? (Level IV)	
1. Was validation restricted to the retrospective use of statistical techniques on the original database? (If so, this is a Level IV rule & is not ready for clinical application) Level IV (These rules have been derived but not validated or have been validated only in split samples, large retrospective databases, or by means of statistical techniques..	Yes. This was a retrospective cohort study. In the derivation for qSOFA, multiple logistic regressions of data (Bayesian information criterion) were used to develop this rule. Data was then validated against another (retrospective) subset of UPMC data, KPNC hospitals, VA system hospitals and 1 hospital each in King County Washington and Germany. The rule was not applied or tested (validated) prospectively.
II. Has the rule been validated? (Level II or III)	
2. Were all-important predictors assessed in the derivation of the prediction guide?	Uncertain. Derivation attempted to include the patient's baseline risk for in-hospital mortality. In testing criterion validity of previously validated SIRS, SOFA, modified LODS, outcomes of in-hospital mortality or ICU length of stay ≥3 days, were assessed against. There were no outcomes measured for long-term sequelae, or length of hospital stay.

	Baseline risk for in-hospital mortality was calculated by: age, sex, race/ethnicity and weighted Charlson comorbidity score as a measurement of chronic comorbidities. No reporting on how they arrived at selecting the 3 components of the qSOFA score. Typically logistical regression analyses helps to assist in defining clinical predictors.
3. Were all important predictors present in significant proportion of the study population?	Maybe not. Baseline characteristics were controlled for. SOFA, LODS and SIRS all previously validated were included. Serial serum lactate levels were not and is considered an important clinical predictor
4. Does the rule make clinical sense?	Mostly. Respiratory rate and BP less than 100 are common to SIRS and "severe sepsis" respectively. The potential confounders (NH patients, intoxicated patients, post-tictal etc.) regarding mental status assessment in ED patients is less clear and not addressed in derivation.
5. Did validation include prospective studies on several different populations from that used to derive it (II), or was it restricted to only one population (III)?	No. The predictive validity of qSOFA was evaluated retrospectively except a relatively small sample in the ALERTS group was prospective. There was very broad validation against a database that included over 4 million patient visits however the vast majority were retrospective
III. How well did the validation study meet the following criteria?	
1. Did the patients represent a wide spectrum of severity of disease?	Uncertain. For ALL encounters outside ICU (our patients) SIRS scores were 1.0, SOFA scores <2.0 and only 2% had lactate >2.0. Their inclusion criteria may be biased towards less ill patients.

2. Was there a blinded assessment of the gold standard?	No. There is no 'gold standard" for the diagnosis of sepsis.
3. Was there an explicit and accurate interpretation of the predictor variables & the actual rule without knowledge of the outcome?	No. qSOFA was derived and tested amongst patient encounters in which infection was already suspected. All validation testing was performed on retrospective studies.
4. Did the results of the assessment of the variables or of the rule influence the decision to perform the gold standard?	NA.
5. How powerful is the rule (in terms of sensitivity & specificity; likelihood ratios; proportions with alternative outcomes; or relative risks or absolute outcome rates)?	Among ICU encounters, the predictive validity for in-hospital mortality was lower for SIRS (AUROC= 0.64; 95% CI 0.62-0.66) and qSOFA (AUROC= 0.66; 95% CI, 0.64-0.68) vs. SOFA (AUROC= 0.74; 95% CI 0.73-0.76) and LODS (AUROC=0.75; 95%CI, 0.73-0.76). Among non-ICU encounters, qSOFA had predictive validity (AUROC 0.81; 95% CI 0.80-0.82) that was greater than SOFA (AUROC= 0.79, 95% CI 0.78-0.80) and SIRS (AUROC= 0.76; 95% CI 0.75-0.77).
III. Has an impact analysis demonstrated change in clinical behavior as a result of using the rule? (Level I)	
1. How well did the study guard against bias in terms of differences at the start (concealed randomization, adjustment in analysis) or as the study proceeded (blinding, co-intervention, loss to follow-up)?	Unable to determine as this is a retrospective review.
2. What was the impact on clinician behavior and patient-important outcomes?	No assessment of impact of using qSofa as this was not a prospective study. It does suggest that qSOFAFor infected patients outside of the ICU, there is an increasing focus on early recognition of sepsis. The qSOFA score uses 3 clinical variables, and if prospectively validated could be a useful tool. The qSOFA and externally validated SOFA scores also had acceptable agreement in the majority of encounters**.**

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Limitations:

1. Retrospective study. Though this is a common data source for derivation of decision rules, there will need to be prospective validation studies before this rule can be broadly applied.
2. Inclusion criteria may have predisposed to including less ill patients

3. qSOFA does not distinguish between chronic and acute organ dysfunction. With our patient population with multiple comorbidities, unknown baseline mental status and chronic disease, it makes this prediction rule less applicable.
4. Lactic acid is widely used as a screening tool for sepsis, but not fully evaluated as a predictor of sepsis in qSOFA. Further inquiry of whether lactic levels could be used for patients with borderline qSOFA values or as a substitute for individual qSOFA variables, needs to be determined.
5. No clinical impact data regarding how application of the rule improves patient outcomes, reduces harms or costs.

Clinical Bottom Line:

1. If validated on large prospective studies, qSOFA is simple, quickly used at bedside and easily applicable at initial patient presentation. From the emergency department (non-ICU setting), the predictive validity for in-hospital mortality and sepsis was greater than SOFA and SIRS. The task force recommends qSOFA in non-ICU settings to consider the possibility of sepsis.
2. Among ICU encounters with suspected infection, the predictive validity for in-patient mortality and sepsis using SOFA and LODS was statistically greater than SIRS and qSOFA. Task force recommends SOFA score of 2 points or more in the ICU encounters with infection as criteria for sepsis.