Original Article

The prediction of early mortality by the ROX index of oxygenation and respiratory rate in diverse Canadian and Ugandan cohorts of unselected patient: a post-hoc retrospective analysis of 80,558 patient observations

J Kellett, FK Sikakulya & CH Nickel

Abstract

Aim: To investigate the association between in-hospital mortality and the ROX index of respiratory rate and oxygenation in diverse cohorts of unselected patient at different prediction windows.

Methods: A retrospective post-hoc analysis of data from a major regional referral Canadian hospital and a low-resource hospital in sub-Saharan Africa.

Results: Four patient cohorts were examined: Canadian medical, surgical and intensive care unit (ICU) patients, and all patients admitted to an African hospital. In all patients in-hospital mortality rose as ROX declined. Apart from ICU patients, ROX had a high discrimination for death within 72 hours. For non-ICU patients the negative predictive value of death within 72 hours for a ROX value <22 ranged from 0.994 to 1.000

Conclusion: In diverse cohorts of unselected patients, the ROX index has a high discrimination for death within 72 hours. However, the index has little or no prognostic value for patient admitted to ICU.

Keywords

ROX index, mortality prediction, early mortality

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Introduction

In 2016 Roca et al proposed an index combining respiratory rate and oxygenation (ROX) to predict the success of oxygen therapy by high-flow nasal cannula (HFNC) in pneumonia patients with acute hypoxemic respiratory failure.[1] A recent meta-analysis has established the value of ROX for the prediction of HFNC failure in COVID-19 patients.[2] However, there are only a few reports of using the index for other purposes, such as predicting the risk of clinical deterioration and/or early death. A ROX index of less than or equal to 10 has been claimed to be an independent prognostic factor for 28-day mortality in patients with sepsis or septic shock[3] and to have greater predictive validity than the National Early Warning Score (NEWS2) for early deterioration in COVID-19 patients using composite outcome measures, which included both death and escalation of care.[4]

The aim of this study was to investigate the association between the ROX index and in-hospital mortality of diverse cohorts of unselected patient at different prediction windows.

Methods

This is a retrospective post-hoc analysis of previously obtained and reported clinical data from a major regional referral Canadian hospital between 2005 and 2010[5] and a low-resource hospital in sub-Saharan Africa between 2016 and 2021.[6]

Databases

Thunder Bay Regional Health Sciences Centre (TBRHSC) is a 375-bed hospital in north-western Ontario, an area of 526,000 thousand square kilometres between Hudson Bay and the north shore of Lake Superior with a population of 250,000. Age, respiratory rate, oxygen saturation, inspired oxygen concentration, length of stay and mortality of every patient >=16 years age admitted to TBRHSC from 1st January 2005 and 31st December 2010 was extracted from the hospital's Meditech system. Since the system only recorded length of stay by the calendar day a patient with a length of stay of one day could have been in hospital for only a few minutes or up to 48 h. How respiratory rates were measured was not documented.

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Kitovu Hospital has 220 beds and is located near Masaka, Uganda, 140km from the capital city of Kampala. It is a Private Not for Profit Hospital, operated by the Uganda Catholic Medical Bureau. The hospital has no intensive care unit and cannot provide invasive ventilation outside its operating theatre. Between 15th July 2016 and 19th July 2021, as part of an ongoing quality improvement project, the clinical status, and vital signs on admission of every patient admitted to the hospital's medical unit have been entered at the bedside using tablet computers into a clinical data management and decision support system (rapid electronic assessment data system [READS], Tapa Healthcare DAC). The system was expanded to the hospital's surgical ward on 17th March 2019. Data entry into the READS system was automatically time and date-stamped, and there can be no missing data as it is impossible to complete a READS assessment without entering all the data required, or to enter values that was outside a plausible range, or to close the assessment without entering the patient's condition at hospital discharge (i.e., dead, or alive). Respiratory rate was measured by tapping on a mobile phone screen as the patient breathed, using a free mobile phone app.[7]

Data analysis

In all cohorts the ROX index was derived from the first oxygen saturation and respiratory rate recorded after hospital admission. ROX, presented to the nearest integer, was calculated by dividing the patient's oxygen saturation, by the inspired oxygen concentration (FiO2), and then by the respiratory rate (e.g., 95% / 0.21 / 16 = 28.3). Descriptive statistics were calculated including means/standard deviations (SD), medians, or percentages. The p value for statistical significance was <0.05 and was tested using Student's t-test and Chi-square analysis. Receiver operator characteristic (ROC) curves were calculated and the area under the curves (AUC) compared according to the method of Hanley and McNeil.[8] The optimal sensitivity and specificity for the prediction of death at prediction windows of 24 hours, 48 hours, 72 hours, 96 hours, 120 hours, 144 hours, and in-hospital mortality was determined by the Youden J statistic (i.e., sensitivity + specificity-1).[9]

Ethical approval

Ethical approval for use of data from TBRHSC was obtained from the Research Ethics Board for Thunder Bay Regional Health Sciences Centre, and for Kitovu Hospital data from the Scientific Committee Kitovu Hospital. The study conforms to the principles outlined in the Declaration of Helsinki.[10] The study is reported in accordance with the STROBE statement.[11]

Results

This study examined four distinct patient cohorts. Kitovu hospital provided 5,899 complete records of patient >=16 years of age, all of which contained complete data; 4976 were from medical and 923 from surgical patients. There was a total of 79,652 hospital admissions to TBRHSC – of these 30,956 (39%) were surgical patients, 46,925 (59%) medical patients and 1771 (2%) were intensive care unit (ICU) patients. Records of oxygen saturation, respiratory rate and inspired oxygen concentration records were incomplete in 4,993 patients, yielding a final TBRHSC study population of 74,659 patients, of whom 44,856 were medical patients never admitted to the hospital's ICU, 28,721 surgical patients never admitted to ICU, and 1,082 patients admitted to ICU.

In all patient cohorts in-hospital mortality rises as ROX declines (Figure 1). All four cohorts had significantly different ages, hospital length of stays, respiratory rates, oxygen saturations, FiO2, and ROX values. The only similarities were the FiO2 values of TBRHSC medical and surgical patients (0.24 SD 0.07 versus 0.24 SD 0.10), the length of hospital stay of medical and intensive care unit patients (9.5 SD 14.5 versus 9.4 SD 16.1 days), and the respiratory rate of Kitovu and intensive care unit patients (22.1 SD 6.0 versus 21.9 SD 7.0 breaths per minute). ICU patients were more likely to be male. The in-hospital mortalities for all four cohorts were significantly different ranging from 0.6% for surgical patients to 51.7% for patients admitted to intensive care. Deaths rates varied significancy at different time after admission. The percent of death occurring within 72

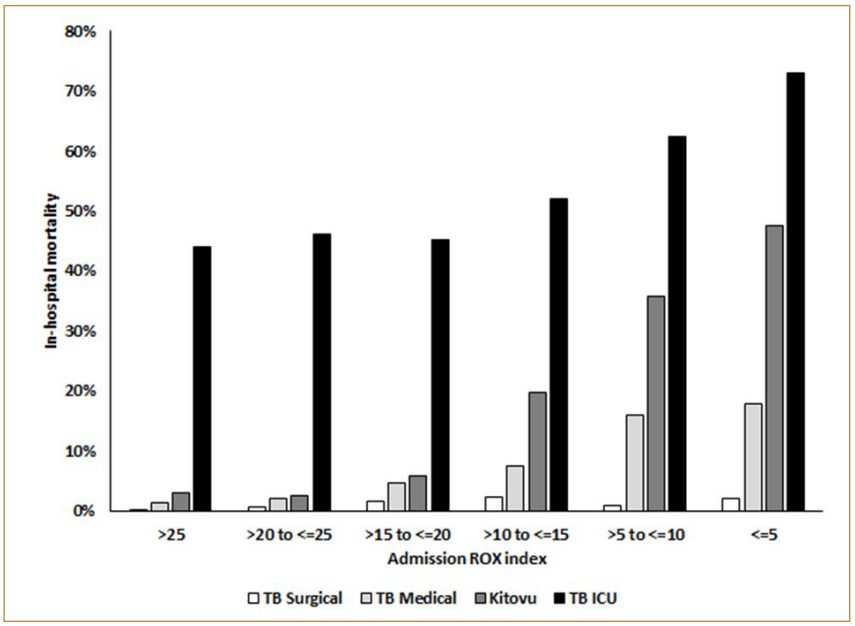

Figure 1. In-hospital mortality according to admission ROX index.
TB = Thunder Bay Regional Health Science Centre.

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Table 1. Differences in sex, ages. hospital length of stay, oxygen saturation, inspired oxygen, respiratory rates, ROX index and mortality between cohorts.

	Thunder Bay		Kitovu	Thunder Bay
Variable	**Medical – ICU excluded**	**Surgical**	**All patients**	**ICU**
n	44856	28721	5899	1082
Male sex	21709 (48.4%) *	13784 (48.0%) *	2807 (47.7%) *	620 (57.3%)
Age (years)				
Mean	67.7SD17.8	57.1 SD 19.1	50.9 SD 21.8	63.8 SD 17.9
Median	71	58	50	67
IQR	56-82	43-72	31-70	53-78
Length of stay (days)				
Mean	9.5 SD 14.5 *	5.4 SD 7.3	4.6 SD 3.8	9.4 SD 16.1 *
Median	6	3	4	4
IQR	3-11	2-6	2-6	2-11
Oxygen saturation (%)				
Mean	96.1 SD 3.7	96.6 SD 3.3	94.7 SD 6.9	95.2 SD 6.6
Median	96	97	96	97
IQR	95-98	96-98	94-98	94-99
Inspired oxygen FiO2				
Mean	0.24 SD 0.07 *	0.24 SD 0.10 *	0.22 SD 0.02	0.35 SD 0.18
Median	0.21	0.21	0.21	0.28
IQR	0.21 - 0.21	0.21 - 0.21	0.21 - 0.21	0.21 - 0.36
Respiratory rate (bpm)				
Mean	19.0 SD 4.5	18.0 SD 3.2	22.1 SD 6.0 *	21.9 SD 7.0 *
Median	18	18	21	20
IQR	18 -20	16-20	18-24	18-25
ROX index				
Mean	23.0 SD 6.2	24.3 SD 5.7	21.5 SD 6.0	16.8 SD 9.1
Median	24.2	25.7	21.5	16.1
IQR	20.0 - 26.2	23.1 - 27.5	18.1 - 24.9	10.4 - 22.8
Mortality				
In-hospital mortality	1364 (3.04%)	178 (0.6%)	369 (6.26%)	559 (51.66%)
24 hours	75 (0.17%) *	9 (0.03%)	16 (0.27%) *	56 (5.18%)
48 hours	131 (0.29%)	12 (0.04%)	82 (1.39%)	84 (7.76%)
72 hours	255 (0.57%)	26 (0.09%)	152 (2.58%)	131 (12.11%)
96 hours	371 (0.83%)	42 (0.15%)	198 (3.36%)	165 (15.25%)
120 hours	461 (1.03%)	52 (0.18%)	244 (4.14%)	192 (17.74%)
144 hours	563 (1.26%)	61 (0.21%)	277 (4.70%)	223 (20.61%)
Ratio deaths within 72hour to all deaths	18.70%	14.61%	41.19%	23.43%

* = indicates cohorts in which there is no significant difference between variables marked

hours of admission ranging from 14.6% for TBRHSC surgical patients to 41.2% for Kitovu patients (Table 1).

The discrimination for death of ROX for all ICU patients was poor at all prediction windows, ranging from an AUC of 0.56 to 0.57. For all other patient cohorts, the AUC ranged from 0.84 to 0.90 for death within 24 hours to 0.67 to 0.74 for in-hospital mortality (Figure 2). Apart from ICU patients, there were no statistical differences in AUC for up to 78 hours after the initial ROX measurement. The Youden J statistic varied from 22 for TBRHSC surgical patients to 13 for Kitovu patients for death within 24 hours. The Youden J statistic was 21 for all prediction windows for TBRHSC medical patients (Table 2).

The performance of a ROX value <22 was determined over prediction windows up to 72 hours

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(Table 3). The proportion of patients with ROX values <22 ranged from 17.3% for TBRHSC surgical patients to 71.7% for ICU patients. Apart from ICU patients, the negative predictive value of a ROX <22 ranged from 0.994 to 1.000.

Discussion

Main findings

This study found that in three markedly different unselected patient populations, the ROX index had a high discrimination for mortality within 72 hours of its measurement. However, the ROX index had poor discrimination and little or no prognostic value for

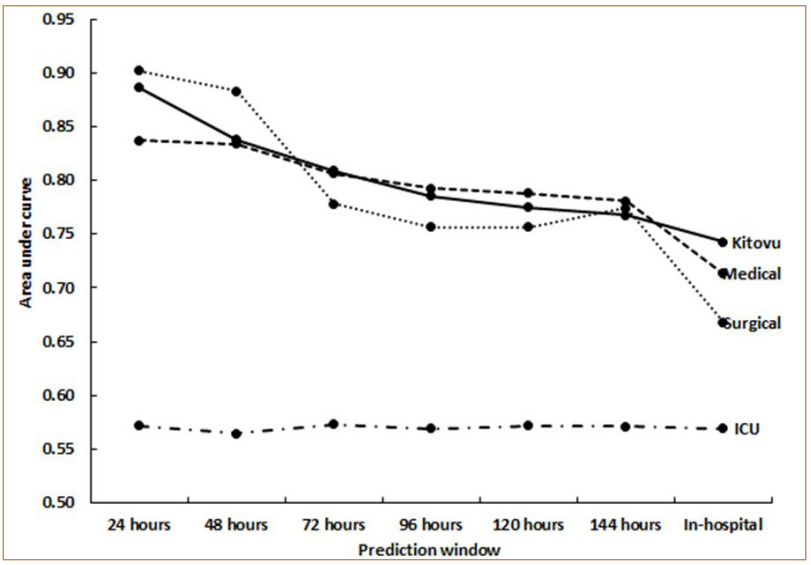

Figure 2. The area under the curve of medical, surgical and intensive care unit patients in Thunder Bay Regional Health Science and all medical and surgical Kitovu Hospital patients at different prediction windows after ROX index measurement.

Table 2. Discrimination of ROX according to cohort and prediction window. There was no significant difference in the area under the receiver operating characteristic curves (AUC) for all patient cohort except ICU patients for prediction windows from 0 to 2 days. The AUC for ICU was significantly lower than for all other patient cohorts and remained unchanged at any prediction window.

Prediction window	Cohort	ROX value with highest Youden statistic	AUC (95%CI)		
24 hours	Medical - excluding ICU	21	0.84	(0.78	- 0.89)
	Surgical	22	0.90	(0.77	- 1.04)
	Kitovu	13	0.89	(0.78	- 0.99)
	ICU	20	0.57	(0.49	*- 0.65)*
48 hours	Medical - excluding ICU	21	0.83	(0.79	- 0.88)
	Surgical	22	0.88	(0.76	- 1.01)
	Kitovu	18	0.84	(0.78	- 0.89)
	ICU	17	0.56	(0.50	*- 0.63)*
72 hours	Medical - excluding ICU	21	0.81	(0.77	- 0.84)
	Surgical	22	0.78	(0.67	- 0.88)
	Kitovu	18	0.81	(0.77	-0.85)
	ICU	16	0.57	(0.52	*- 0.63)*
96 hours	Medical - excluding ICU	21	0.79	(0.77	- 0.82)
	Surgical	22	0.76	(0.67	- 0.84)
	Kitovu	15	0.79	(0.75	- 0.82)
	ICU	15	0.57	(0.52	*- 0.62)*
120 hours	Medical - excluding ICU	21	0.79	(0.76	- 0.81)
	Surgical	22	0.76	(0.67	- 0.84)
	Kitovu	15	0.77	(0.74	- 0.81)
	ICU	15	0.57	(0.53	*- 0.62)*
144 hours	Medical - excluding ICU	21	0.78	(0.76	- 0.80)
	Surgical	22	0.77	(0.71	- 0.84)
	Kitovu	15	0.77	(0.73	- 0.80)
	ICU	15	0.57	(0.53	*- 0.61)*
In-hospital	Medical - excluding ICU	21	0.71	(0.70	- 0.73)
	Surgical	22	0.67	(0.62	- 0.71)
	Kitovu	17	0.74	(0.71	- 0.77)
	ICU	15	0.57	(0.54	*- 0.60)*

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Table 3. Performance of a cut-off of ROX <22 at different prediction windows.

Prediction window	Cohort	Sensitivity	Specificity	PPV	NPV	LR+ve	LR-ve	Proportion patients ROX <22	Odds ratio mortality ROX <22 (95% CI)		
24 hours	Surgical	0.89	0.83	0.002	1.000	5.16	0.13	17.3%	38.42	(4.87	- 833.24)
	Medical - ICU excluded	0.87	0.70	0.005	1.000	2.88	0.19	30.2%	15.11	(7.47	- 31.48)
	Kitovu	0.94	0.48	0.005	1.000	1.80	0.13	52.1%	13.83	(1.91	- 285.77)
	ICU	0.91	0.29	0.066	0.984	1.29	0.30	71.7%	4.23	(1.59	- 12.28)
48 hours	Surgical	0.75	0.83	0.002	1.000	4.35	0.30	17.3%	14.41	(3.56	- 67.77)
	Medical - ICU excluded	0.87	0.70	0.008	1.000	2.90	0.19	30.2%	15.65	(9.15	- 27.13)
	Kitovu	0.91	0.48	0.024	0.998	1.77	0.18	52.1%	10.05	(4.43	- 24.03)
	ICU	0.86	0.29	0.093	0.961	1.22	0.48	71.7%	2.51	(1.29	- 4.97)
72 hours	Surgical	0.62	0.83	0.003	1.000	3.57	0.46	17.3%	7.69	(3.28	- 18.34)
	Medical - ICU excluded	0.82	0.70	0.015	0.999	2.74	0.26	30.2%	10.67	(7.64	- 14.93)
	Kitovu	0.89	0.49	0.044	0.994	1.74	0.23	52.1%	7.58	(4.44	- 13.10)
	ICU	0.86	0.30	0.144	0.938	1.22	0.48	71.7%	2.55	(1.49	- 4.39)

PPV = positive predictive value, NPV = negative predictive value, LR+ve = positive likelihood ration, LR-ve = negative likelihood ratio, 95%CI = 95% confidence interval.

patient admitted to ICU. Although the optimal cut-off value for ROX may vary in different patient populations, outside of ICU, all patients with a ROX >=22 have a very low risk of early death.

Limitations

This is a retrospective analysis, which includes historical data collected prior to the COVID-19 pandemic. To simplify analysis, ROX values were reduced to the nearest integer. Since the TBRHSC Meditech system only recorded length of stay by the calendar day a patient with a length of stay recorded as less than 24 hours could have been in hospital for only a few minutes or up to 48 h. The length of time patients spent in either hospital's emergency department before admission was not available. No data on follow-up after hospital discharge was available. Up to a quarter of patients were discharged within 2-3 days, so some patients might have died shortly after leaving the hospital. It is not clear what, if any, criteria were used to provide patients with supplemental oxygen in any of the cohorts or determine the accuracy of oxygen saturation measurements. However, any such errors would have been random.

The ROX index depends on respiratory rate measurements, which are often inaccurate.[12-14] In Kitovu Hospital respiratory rate was measured by a computer algorithm contained in a free mobile phone app, which has been shown to measure respiratory rate accurately and reliably in acutely ill patients within approximately 15 seconds.[7] In TBRHSC the technique of respiratory rate measurement was not documented, and probably varied. Although machine measured values have been reported to be the best predictors of mortality,[15] others have found that manual recordings may be better because they are biased by the nurse's more accurate intuitive judgement of how sick the patient is.[16]

Interpretation

Our findings support those of Prower et al,[4] who in 1,122 COVID-19 patients reported the AUC of a composite outcome of cardiac arrest, unplanned critical care admission or death within 24 hours was 0.848 (95% CI 0.837-0.858) for the ROX index, compared with 0.815 (95% CI 0.804-0.826) for the National Early Warning Score (NEWS2). They also found that an optimal ROX value of 14.91 identified deterioration four hours earlier than a NEWS2 optimal value of 5.

Hypoxia and hypoperfusion are the usual antecedents of death, and sustained hypoxia commonly causes a viscous cycle of circulatory failure, hypoperfusion and tissue hypoxia, which results in death if not reversed.[17] The support of ventilation provided by intensive care can usually correct hypoxia, albeit only temporarily in some patients. This probably explains the poor discrimination of the ROX index for early death in ICU patients.

Clinical relevance

Our findings show, that in all patient populations outside of ICU, the risk of early death rises as ROX declines. However, the optimal ROX value for clinical intervention may not correspond to the highest Youden statistic for death. Roca reported a

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ROX <2.85, <3.47, and <3.85 at 2, 6, and 12 hours of HFNC initiation, respectively, were predictors of HFNC failure.[18] A ROX <=10 predicted 28-day mortality in patients with sepsis,[3] and Prower *et al* found that a ROX value of 14.91 identified deterioration four hours earlier than NEWS2.[4]

Unlike early warning scores, which require a complete set of vital signs that take time to measure and calculate,[19] the ROX index only requires an oximeter and can be quickly and repeatedly determined. Therefore, ROX may be particularly valuable in low-resource settings and for frequently monitoring post-operative patients; levels falling below 22 causing increasing concern.

Conclusion

In diverse cohorts of unselected patients, the ROX index has a high discrimination for death within 72 hours. However, the index has little or no prognostic value for patient admitted to ICU.

Declaration of competing interest

All costs were borne by the authors. John Kellett is a major shareholder, director, and chief medical officer of Tapa Healthcare DAC. The other authors have no potential conflicts of interest.

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Abbreviations

95%CI = 95% confidence interval
AUC = area under the curves
HFNC = high-flow nasal cannula
ICU = intensive care unit
NEWS2 = National Early Warning Score 2
READS = Rapid Electronic Assessment Data System
ROC = Receiver operator characteristic curves
SD = standard deviation
TBRHSC = Thunder Bay Regional Health Science Centre

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