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The National Early Warning Score (NEWS2) systematically underestimates the risk of in-hospital mortality in unplanned COVID-19 admissions to hospital.

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Abstract

Objectives: Although the National Early Warning Score (NEWS) and its latest version NEWS2 are recommended for monitoring for deterioration in patients admitted to hospital, little is known about their performance in COVID-19 patients. We aim to compare the performance of National Early Warning Score (NEWS2) during the first phase of the COVID-19 pandemic.

Design: a retrospective cross-sectional study

Setting: Two acute hospitals (Scarborough and York) are combined into a single dataset and analysed collectively.

Participants: Adult (>=18 years) non-elective admissions discharged between 11-March-2020 to 13-June-2020 with an index NEWS2 electronically recorded within ±24 hours of admission are used to predict mortality at four time points (in-hospital, 24hours, 48hours, and 72hours) in COVID-19 versus non-COVID-19 admissions.

Results: Out of 6480 non-elective admissions, 620 (9.6%) had a diagnosis of COVID-19. They were older (73.3 vs 67.7yrs), more often male (54.7% vs 50.1%), had higher index NEWS (4 vs 2.5) and NEWS2 (4.6 vs 2.8) scores and higher in-hospital mortality (32.1% vs 5.8%). The c-statistics for predicting in-hospital mortality in COVID-19 admissions was significantly lower using NEWS (0.64 vs 0.74) or NEWS2 (0.64 vs 0.74), however these differences reduced at 72hours (NEWS: 0.75 vs 0.81; NEWS2: 0.71 vs 0.81), 48 hours (NEWS: 0.78 vs 0.81; NEWS2: 0.76 vs 0.82) and 24hours (NEWS: 0.84 vs 0.84; NEWS2: 0.86 vs 0.84). Increasing NEWS2 values reflected increased mortality, but for any given value the absolute risk was on average 24% higher (e.g.NEWS2=5: 36% vs 9%).

Conclusions: NEWS2 is a valid predictor of the mortality risk but substantially underestimates the absolute mortality risk in COVID-19 patients. Clinical staff and escalation protocols based on NEWS2 need to make note of this finding.

Key words: NEWS, NEWS2, COVID-19, mortality risk, early warning scores

Article Summary

- This study compares the performance of National Early Warning Score (NEWS2) during the first phase of the COVID-19 pandemic.
- Although we found no evidence of NEWS2 as having superior performance to NEWS this does suggest that the additional enhancements in NEWS2 are having limited impact and the underlying reasons needs further study.
- This is a data from a single NHS Trust and the extent to which these findings, especially to populations with a higher proportions of minority ethnic groups because of the higher mortality associated with these groups, is required.
- Nonetheless, NEWS2 is repeatedly updated for each patient according to local hospital protocols, and the extent to which changes in NEWS2 over time reflect changes in mortality risk needs further study.

Introduction

The novel coronavirus SARS-19, which was declared as a pandemic on 11-March 2020, produces the newly identified disease 'COVID-19' in patients with symptoms (Coronaviridae Study Group of the International Committee on Taxonomy of Viruses[1]) which has challenged health care systems worldwide.

COVID-19 patients admitted acutely to hospital can develop severe disease with life threatening respiratory and/or multi-organ failure [2,3] with a high risk of mortality in part due to the lack of an effective treatment (bar supportive care) for the underlying disease. Thus, it is recommended that patients at risk of deterioration are referred to critical care. The appropriate early assessment and management of patients with COVID-19 is important in ensuring high-quality care, whether that includes effective isolation, escalation to critical care, ward level care or the need for high quality palliative care.

In the UK National Health Service (NHS), the patient's vital signs are monitored and summarised into a National Early Warning Score (NEWS) or its latest iteration (NEWS2)[4]. NEWS is used the world over[4]. NEWS and NEWS2 are derived from six physiological variables or vital signs—respiration rate, oxygen saturations, temperature, systolic blood pressure, heart rate and level of consciousness (alert, confusion, voice, pain, unresponsive) and also use of supplemental oxygen—which are routinely collected by nursing staff as an integral part of the process of care, usually for all patients, and then repeated thereafter depending on local hospital protocols. NEWS2 includes two oxygen saturation scales (scale 1 and scale 2) and new confusion[5]. NEWS2 points are allocated according to basic clinical observations and the higher the NEWS2 the more likely it is that the patient is deteriorating.

Although NEWS2 is recommended for use in COVID-19 patients[6], little is known about how NEWS2 performs in practice. In this study, we aimed to compare the performance of NEWS2 (and NEWS) in unplanned admissions to a teaching hospital during the first phase of the novel coronavirus SARS Cov-2 (COVID-19) pandemic in predicting in-hospital mortality at four time points (24hours, 48hours,72hours and in-hospital mortality) in COVID-19 versus non-COVID-19 admissions.

Methods

Setting & data

Our cohort of unplanned admissions are from two acute hospitals which are approximately 65 kilometres apart in the Yorkshire & Humberside region of England – Scarborough hospital (n~300 beds) and York Hospital (YH) (n~700 beds), managed by York Teaching Hospitals NHS Foundation Trust. For the purposes of this study, the two acute hospitals are combined into a single dataset and analysed collectively. The hospitals have electronic NEWS2 scores and vital signs recording which are routinely collected as part of the patient's process of care.

We considered all adult (age≥18 years) unplanned admissions to medicine, elderly and general surgery (excluding ambulatory care area patients), discharged during a 3-month period (11 March 2020 to 13 June 2020), with electronic NEWS2 recorded within ±24 hours of admission. For each emergency admission, we obtained a pseudonymised patient identifier, patient's age (years), gender (male/female), ethnicity, body mass index (BMI kg/m^2), discharge status (alive/dead), admission and discharge date and time, diagnoses codes based on the 10th revision of the International Statistical Classification of Diseases (ICD-10), NEWS2(2) (including its subcomponents respiratory rate, temperature, systolic pressure, pulse rate, oxygen saturation, oxygen supplementation, oxygen scales 1 & 2, and alertness including confusion). The diastolic blood pressure was recorded at the same time as systolic blood pressure. Historically, diastolic blood pressure has always been a routinely collected physiological variable on vital sign charts and is still collected where electronic observations are in place. NEWS2 produces integer values that range from 0 (indicating the lowest severity of illness) to 23 (the maximum NEWS2 value possible). The index (f NEWS2 was defined as the first electronically recorded NEWS2 within ±24 hours of the admission time. We excluded records where the first NEWS2 was not within ±24 hours of admission or was missing/not recorded (see Table 1). The ICD-10 code 'U071' was used to identify records with COVID-19. We searched, primary and secondary ICD-10 codes for 'U071' for identifying COVID-19.

Statistical Modelling

We began with exploratory analyses including line plots that showed the relationship between age, vital signs, NEWS2 and risk of in-hospital death in COVID-19 and non-COVID-19. We compared the continuous covariates using a two-sample independent t-test (for normal data) or Wilcoxon rank sum test (for non-normal data). We compared the categorical covariates using a Chi-square proportion test. P-values less than 0.05 were defined as statistically significant.

We determined the discrimination of NEWS2. Discrimination relates to how well a model can separate, (or discriminate between), those who died and those who did not. The concordance statistic (c-statistic) is a commonly used measure of discrimination. For a binary outcome (alive/died), the c-statistic is the area under the Receiver Operating Characteristics (ROC) curve. The ROC curve is a plot of the sensitivity, (true positive rate), versus 1-specificity, (false positive rate), for consecutive predicted risks. A c-statistic of 0.5 is no better than tossing a coin, whilst a perfect model has a c-statistic of 1. In general, values less than 0.7 are considered to show poor discrimination, values of 0.7 to 0.8 can be described as reasonable, and values above 0.8 suggest good discrimination[7]. We developed two separate logistic regression models for predicting in-hospital mortality with NEWS and NEWS2 as covariates respectively. We assessed their performance in predicting the mortality at four specified time points - 24hour, 48hour, 72hour and in-hospital in COVID-19 and non-COVID-19 patients using the c-statistic. We assessed the sensitivity, specificity, positive predictive value, negative predictive value and likelihood ratios for NEWS and NEWS2 at values ≥5 which is the usual threshold value for escalation to critical care. The 95% confidence interval for the c-statistic was derived using DeLong's method as implemented in the *pROC* library [8] in R [9]. All analyses were undertaken using *R* [9] and Stata [10].

Since NEWS2 extends NEWS, we used the same dataset to compare NEWS and NEWS2 especially as NEWS is still in widespread use.

Ethical Approval

This study used de-identified data and received ethical approval from Health Research Authority (HRA) and Health and Care Research Wales (HCRW) (reference number 19/HRA/0548).

Patient and Public Involvement:

No patient involved

Results

Cohort description

There were 6480 discharges over a 3-month period. We excluded 36 (0.6%) records because the index NEWS2 was not recorded within ±24 hours of the admission date/time or NEWS2 was missing or no recorded at all (see Table S1 in supplementary material).

We analysed data from 6444 admissions, of which 9.6% (620/6444) were diagnosed COVID-19. The demographic, vital signs and outcome profiles of the COVID-19 versus non-COVID-19 admissions is shown in Table 1 and Figure 1. COVID-19 admissions were older (73.3 vs 67.7, p<0.001), more likely to be male (54.7% vs 50.1%, p<0.001), with higher BMI (kg/m2) (27.5 vs 26, p<0.001) than non-COVID-19 admissions. COVID-19 admissions had higher index NEWS (4 vs 2.5, p<0.001) and index NEWS2 (4.6 vs 2.8, p<0.001) than non-COVID-19 admissions which was reflected in differences in vital signs notably, a higher respiratory rate (23.5 vs 19.8, p<0.001), lower oxygen saturation (94.8% v 96.4%, p<0.001), higher oxygen supplementation (33.4% vs 11.5%, p<0.001), lower systolic blood pressure (136.1 mmHg vs 142.5 mm Hg, p<0.001) and less likely to be alert (82.9% vs 90%, p<0.001). COVID-19 admissions were more likely to be referred to the critical outreach team (14.7% vs 3.6%, p<0.001), admitted to the intensive care unit (ICU) (6.8% vs 2.5%) and referred to palliative care (10.5% vs 4.9%). COVID-19 admissions had longer hospital stay (7.3 days vs 3 days, p<0.001) and higher in-hospital mortality (32.1% vs 5.8%, p<0.001).

Figure 2 shows the relationship between continuous covariates and the observed risk of in-hospital mortality in COVID-19 versus non-COVID-19 admissions. Whilst the pattern of mortality was broadly similar between COVID-19 and non-COVID-19 admissions, COVID-19 admissions had a consistently higher risk of mortality for the range of covariate values. Although increasing NEWS and NEWS2 scores reflected increased mortality, but for any given value of NEWS or NEWS2 the risk of mortality for COVID-19 was on average 24% higher and at a NEWS or NEWS2 of 5 the risk of mortality in COVID-19 vs Non-COVID-19 was 36% versus 9%.

The performance of index NEWS2 to predict the risk of death (24hour, 48hour, 72hour, in-hospital) in COVID-19 and non-COVID-19 emergency medical admissions is shown in the supplementary Table S3 and Figure 3. The c-statistics for predicting in-hospital mortality in COVID-19 admissions was significantly lower using (NEWS: 0.64 vs 0.74; NEWS2: 0.64 vs 0.74), however these differences reduced at 72hours (NEWS: 0.75 vs 0.81; NEWS2: 0.71 vs 0.81), 48 hours (NEWS: 0.78 vs 0.81; NEWS2: 0.76 vs 0.82) and 24hours (NEWS: 0.84 vs 0.84; NEWS2: 0.86 vs 0.84).

Table S3 includes the sensitivity, specificity, positive and negative predictive values for NEWS and NEWS2 for COVID-19 and non-COVID-19 patients. NEWS2 had a higher sensitivity but lower specificity compared to NEWS.

Characteristic	COVID-19	Non-COVID-19	p-value
N	620	5824	-
Male (%)	339 (54.7)	2918 (50.1)	0.033
Mean Age [years] (SD)	73.3 (15.4)	67.7 (19)	<0.001
Ethnicity			<0.001
British	465 (75)	4668 (80.2)	
Black, Asian, and other minority ethnic	34 (5.5)	152 (2.6)	
Missing	121 (19.5)	1004 (17.2)	
Median BMI (IQR)* [kg/m^2]	27.5 (8.4)	26 (7.6)	<0.001
Mean NEWS (SD)	4 (2.8)	2.5 (2.3)	<0.001
Mean NEWS2 (SD)	4.6 (3)	2.8 (2.7)	<0.001
Vital Signs			
Mean Respiratory rate [breaths per minute] (SD)	23.5 (6.6)	19.8 (5)	<0.001
Mean Temperature [oC] (SD)	36.8 (1.1)	36.3 (0.9)	<0.001
Mean Systolic pressure [mmHg] (SD)	136.1 (25.8)	142.5 (29.2)	<0.001
Mean Diastolic pressure [mmHg] (SD)	76.5 (16.3)	79.4 (16.8)	<0.001
Mean Pulse rate [beats per minute] (SD)	92.2 (22.1)	88.5 (22.2)	<0.001
Mean % Oxygen saturation (SD)	94.8 (4.4)	96.4 (2.9)	<0.001
Oxygen supplementation (%)	207 (33.4)	667 (11.5)	<0.001
Mean oxygen flow rate (SD)	7.6 (5.8)	6.4 (5.5)	0.008
Oxygen scale 2 (%)	42 (6.8)	361 (6.2)	0.634
Alertness			<0.001
Alert (%)	514 (82.9)	5239 (90)	
Baseline confusion (%)	5 (0.8)	45 (0.8)	
New confusion (%)	19 (3.1)	82 (1.4)	
Pain (%)	0 (0)	49 (0.8)	
Voice (%)	58 (9.4)	227 (3.9)	
Unconscious (%)	24 (3.9)	182 (3.1)	
Critical outreach team (%)	91 (14.7)	211 (3.6)	<0.001
Admission to ICU (%)	42 (6.8)	147 (2.5)	<0.001
Palliative care (%)	65 (10.5)	288 (4.9)	<0.001
On ventilation (%)	18 (2.9)	12 (0.2)	<0.001
Median Length of Stay (days) (IQR)	7.3 (11.7)	3 (5.5)	<0.001
Mortality with-in 24 hours (%)	9 (1.5)	53 (0.9)	0.273
Mortality with-in 48 hours (%)	15 (2.4)	94 (1.6)	0.189
Mortality with-in 72 hours (%)	33 (5.3)	131 (2.3)	<0.001
In-hospital Mortality	199 (32.1)	336 (5.8)	<0.001

Table 1 Characteristics of emergency medical admissions in COVID-19 versus non-COVID-19

** BMI is missing 188 (30.3%) for COVID and 2283 (39.2%) for Non-COVID*

Discussion

We have found that while NEWS2 is a valid predictor of in-hospital mortality, it systematically underestimates the risk of in-hospital mortality in unplanned COVID-19 admissions by an average of 24%, compared to non-COVID-19 admissions. These findings were also seen in NEWS and to a large extent were reflected in the profile of the underlying vital signs data. The World Health Organisation (WHO) describes the range of symptoms seen in COVID-19[16] which include (but are not limited to) dyspnoea, reduced alertness, delirium, fever, tachypnoea and hypoxia (as a common sign in moderate to severe disease). All of which are reflected in the physiological observation set underpinning NEWS and NEWS2 and were more frequent in our COVID-19 patients compared to non-COVID-19 patients. Nevertheless, we also found evidence of lower blood pressure and higher pulse rate in COVID-19 patients. Furthermore, there appeared to be no clear advantage of NEWS2 over NEWS in our study.

Whilst guidelines for using NEWS and NEWS2 have emphasised the importance of clinical judgement when using these scoring systems, the systematic underestimation of mortality in unplanned COVID-19 admissions has not previously been reported. This needs to be brought to the attention of medical and nursing staff and reflected in escalation protocols and guidelines to mitigate any potential threats to patient safety by promoting situational awareness about the actual mortality risk for COVID-19 patients. The NEWS2 guidelines[6] do note that patients with COVID-19 can develop 'silent hypoxia' where oxygen saturations can drop to low levels and precipitate acute respiratory failure quickly without the presence of obvious symptoms of respiratory distress. As such any patients admitted and on supplemental oxygen may develop a rapidly increasing oxygen requirement that may not result in an increase in the NEWS2 score. It is stressed that any increase in oxygen requirement should trigger an escalation for review by a competent senior decision maker[6].

Consideration should be also be given to enhancing NEWS or NEWS2 so that they can be used in COVID-19 and non-COVID-19 patients rather than needing to change scoring systems or adjust estimations of risk dependent on diagnosis. We have previously demonstrated how a fully automated computer enhanced NEWS score can be developed which requires no additional data collection and builds on the standardisation provided by NEWS[11]. We now propose to extend this to include COVID-19 status.

There are several limitations to our study. (1) This is a data from a single NHS Trust and the extent to which these findings, especially to populations with a higher proportions of minority ethnic groups because of the higher mortality associated with these groups, is required. (2) We used the index NEWS2 which reflects the 'on-admission' risk of mortality of the patients. Nonetheless, NEWS2 is repeatedly updated for each patient according to local hospital protocols, and the extent to which changes in NEWS2 over time reflect changes in mortality risk needs further study. (3) Although we found no evidence of NEWS2 as having superior performance to NEWS this does suggest that the additional enhancements in NEWS2 are having limited impact and the underlying reasons needs further study. Nevertheless it is worth noting that a recent, albeit small Italian study based on 71 hospitalised COVID-19 patients found NEWS2 to be a good predictor (with a high c-statistic 0.90) of subsequent ICU admission for COVID-19 patients but was not able to consider mortality because of insufficient events[12].

Conclusions

NEWS2 and NEWS predict mortality in COVID-19 patients in addition to non-COVID-19 patients but significantly underestimate the mortality risk at equivalent values in COVID-19 patients. Clinical staff and escalation protocols based on NEWS2 or NEWS need to take note of this finding.

Contributorship

DR & MAM had the original idea for this work. MF undertook the statistical analyses with guidance from MAM. MFi & KB extracted the necessary data frames. DR gave a clinical perspective. DR, MF and MAM wrote the first draft of this paper and all authors subsequently assisted in redrafting and have approved the final version.

Competing Interests

The authors declare no conflicts of interest.

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Data Availability Statement

Our data sharing agreement with NHS York hospital trust does not permit us to share this data with other parties. Nonetheless if anyone is interested in the data, then they should contact the R&D offices in the first instance.

Figure 1 Boxplots without outliers for continuous covariates for COVID-19 versus Non-COVID-19 admissions

Figure 2 Line plots showing the observed risk of in-hospital mortality with continuous covariates for COVID-19 (black colour) and Non-COVID-19 (grey colour) admissions.

Note: Size of circles reflects sample size independently in the COVID-19 and non-COVID-19 groups.

Figure 3 Receiver Operating Characteristic curve for NEWS2 and NEWS in predicting the risk of in-hospital mortality, mortality within 24 hours, 48 hours, and 72 hours in the COVID-19 (black colour) and Non-COVID-19 (grey colour) admissions.

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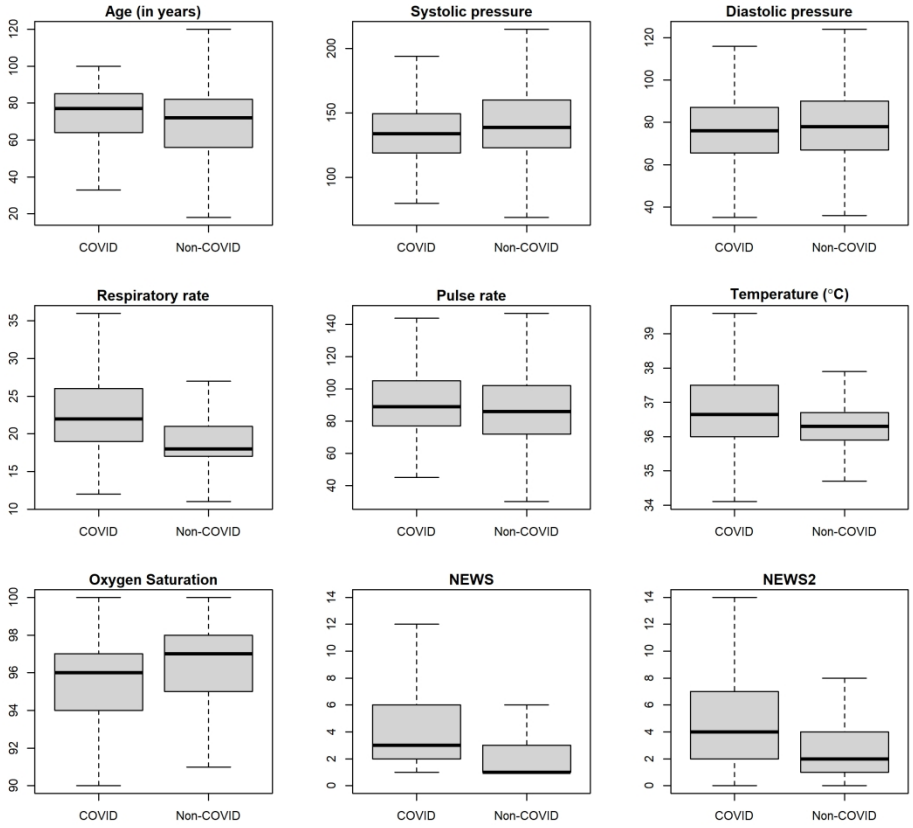

Boxplots without outliers for continuous covariates for COVID-19 versus Non-COVID-19 admissions

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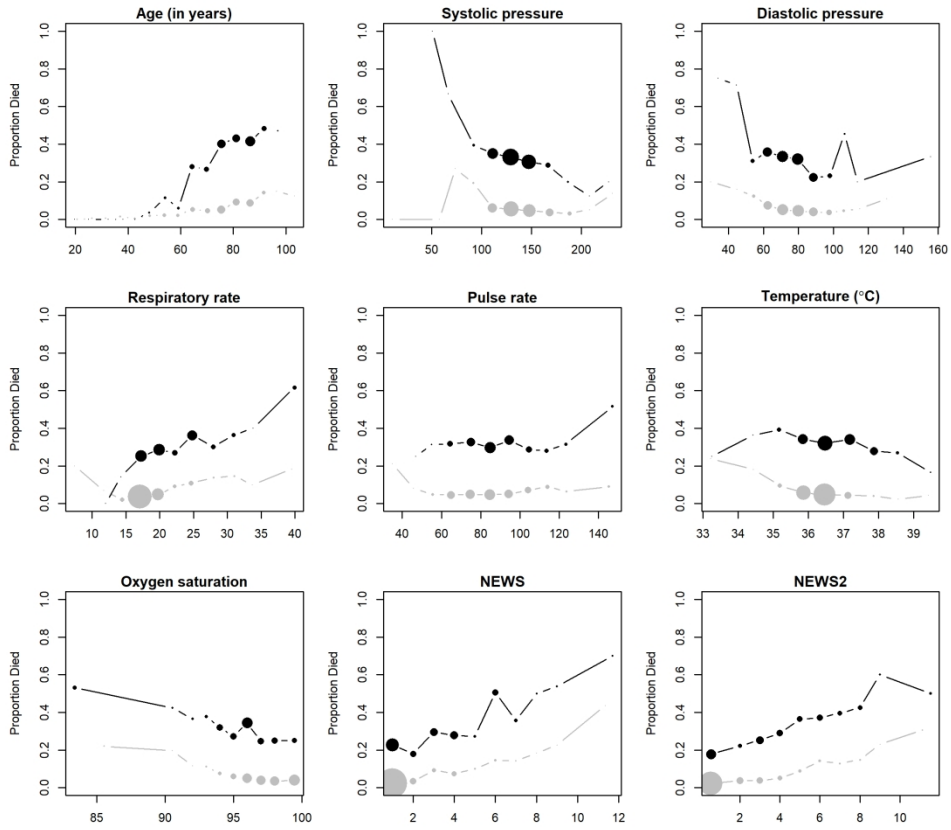
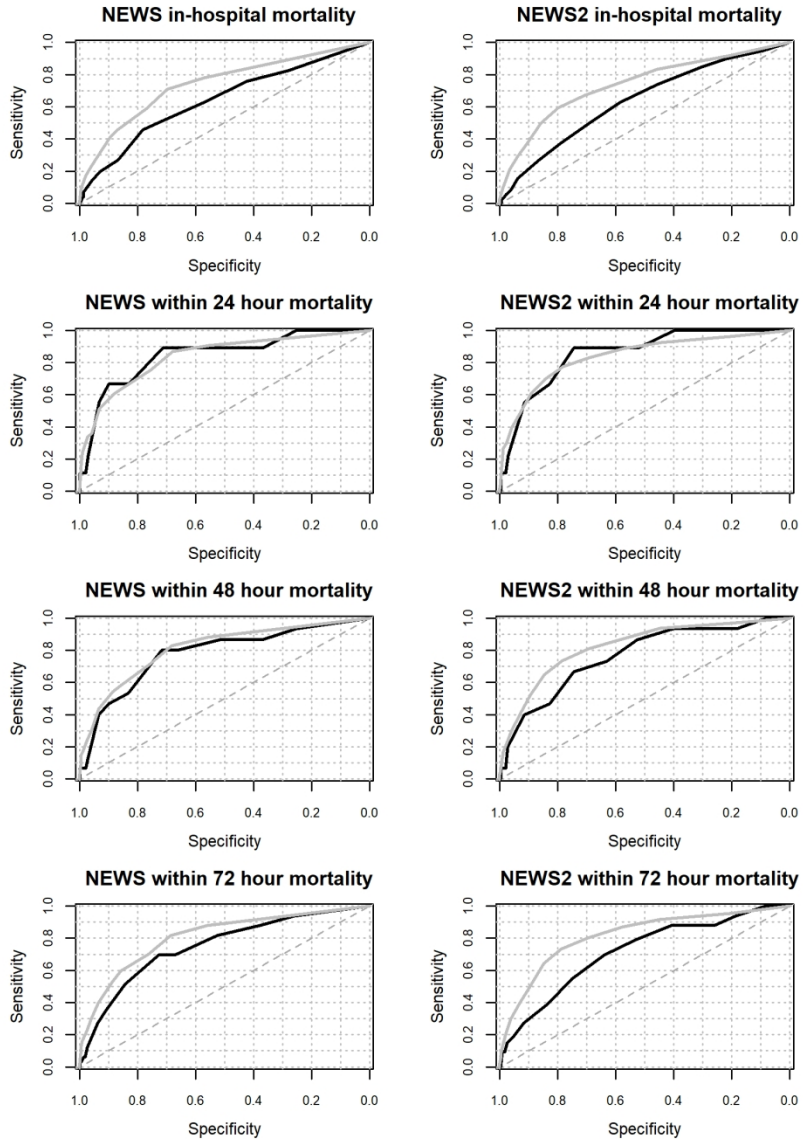


Line plots showing the observed risk of in-hospital mortality with continuous covariates for COVID-19 (black colour) and Non-COVID-19 (grey colour) admissions.
Note: Size of circles reflects sample size independently in the COVID-19 and non-COVID-19 groups.

228x203mm (300 x 300 DPI)



Receiver Operating Characteristic curve for NEWS2 and NEWS in predicting the risk of in-hospital mortality, mortality within 24 hours, 48 hours, and 72 hours in the COVID-19 (black colour) and Non-COVID-19 (grey colour) admissions.

152x203mm (300 x 300 DPI)

Characteristic	COVID-19	Non-COVID-19	All
	N (%)	N (%)	N (%)
Total emergency medical discharges between 11 Mar 20 to 13 June 20	622 (9.6%)	5858 (90.4%)	6480 (100%)
Excluded: No NEWS recorded (%)	0 (0.0)	19 (0.3)	19 (0.3)
Excluded: First NEWS after 24 hours of admission (%)	2 (0.3)	15 (0.3)	17 (0.3)
Total excluded (%)	2 (0.3)	34 (0.6)	36 (0.6)
Total included (%)	620 (99.7)	5824 (99.4)	6444 (99.4)

Table S1 Number of emergency medical admissions included/excluded

Mortality timepoint		COVID-19				Non-COVID-19			
	Model	Risk discharged alive	Risk discharged deceased	Risk Difference	AUC (95% CI)	Risk discharged alive	Risk discharged deceased	Risk Difference	AUC (95% CI)
In-hospital Mortality	NEWS	0.11	0.16	0.06	0.64 (0.59 to 0.69)	0.07	0.17	0.09	0.74 (0.71 to 0.77)
	NEWS2	0.11	0.15	0.04	0.64 (0.59 to 0.68)	0.07	0.16	0.09	0.74 (0.71 to 0.77)
Mortality with-in 24 hours	NEWS	0.12	0.32	0.20	0.84 (0.7 to 0.99)	0.08	0.25	0.17	0.84 (0.78 to 0.89)
	NEWS2	0.12	0.28	0.16	0.86 (0.75 to 0.97)	0.08	0.24	0.16	0.84 (0.78 to 0.9)
Mortality with-in 48 hours	NEWS	0.12	0.26	0.14	0.78 (0.65 to 0.91)	0.08	0.22	0.14	0.81 (0.77 to 0.86)
	NEWS2	0.12	0.23	0.11	0.76 (0.64 to 0.89)	0.08	0.21	0.14	0.82 (0.78 to 0.87)
Mortality with-in 72 hours	NEWS	0.12	0.23	0.11	0.75 (0.66 to 0.84)	0.08	0.214	0.13	0.81 (0.77 to 0.85)
	NEWS2	0.12	0.21	0.09	0.71 (0.62 to 0.8)	0.08	0.21	0.13	0.82 (0.78 to 0.85)

Table S2 Area under the Receiver Operating Characteristic curve in predicting mortality (in-hospital, 24hour, 48hour, 72hour) at index NEWS2 (or NEWS) ≥ 5 in COVID-19 and Non-COVID-19 emergency medical admissions

Mortality type	Models	COVID-19							Non-COVID-19						
		N*	Sensitivity%	Specificity%	PPV	NPV	LR+	LR-	N*	Sensitivity%	Specificity%	PPV	NPV	LR+	LR-
In-hospital	NEWS	183	45.7 (38.7 to 52.9)	78.1 (73.9 to 82)	49.7 (42.3 to 57.2)	75.3 (71 to 79.3)	2.1 (1.7 to 2.6)	0.7 (0.6 to 0.8)	710	40.8 (35.5 to 46.2)	89.6 (88.7 to 90.4)	19.3 (16.5 to 22.4)	96.1 (95.5 to 96.6)	3.9 (3.4 to 4.5)	0.7 (0.6 to 0.7)
In-hospital	NEWS2	300	62.8 (55.7 to 69.5)	58.4 (53.6 to 63.2)	41.7 (36 to 47.5)	76.9 (71.9 to 81.4)	1.5 (1.3 to 1.8)	0.6 (0.5 to 0.8)	1300	59.2 (53.8 to 64.5)	79.9 (78.9 to 81)	15.3 (13.4 to 17.4)	97 (96.4 to 97.5)	3 (2.7 to 3.3)	0.5 (0.4 to 0.6)
Within 24 hours	NEWS	183	88.9 (51.8 to 99.7)	71.4 (67.6 to 74.9)	4.4 (1.9 to 8.4)	99.8 (98.7 to 100)	3.1 (2.4 to 4)	0.2 (0 to 1)	710	60.4 (46 to 73.5)	88.3 (87.4 to 89.1)	4.5 (3.1 to 6.3)	99.6 (99.4 to 99.7)	5.1 (4.1 to 6.5)	0.4 (0.3 to 0.6)
Within 24 hours	NEWS2	300	88.9 (51.8 to 99.7)	52.2 (48.2 to 56.2)	2.7 (1.2 to 5.2)	99.7 (98.3 to 100)	1.9 (1.5 to 2.4)	0.2 (0 to 1.4)	1300	77.4 (63.8 to 87.7)	78.2 (77.1 to 79.2)	3.2 (2.3 to 4.3)	99.7 (99.5 to 99.9)	3.5 (3 to 4.1)	0.3 (0.2 to 0.5)
Within 48 hours	NEWS	183	80 (51.9 to 95.7)	71.7 (68 to 75.3)	6.6 (3.4 to 11.2)	99.3 (98 to 99.9)	2.8 (2.1 to 3.8)	0.3 (0.1 to 0.8)	710	54.3 (43.7 to 64.6)	88.5 (87.6 to 89.3)	7.2 (5.4 to 9.3)	99.2 (98.9 to 99.4)	4.7 (3.9 to 5.8)	0.5 (0.4 to 0.6)
Within 48 hours	NEWS2	300	86.7 (59.5 to 98.3)	52.6 (48.5 to 56.6)	4.3 (2.3 to 7.3)	99.4 (97.8 to 99.9)	1.8 (1.5 to 2.3)	0.3 (0.1 to 0.9)	1300	73.4 (63.3 to 82)	78.5 (77.4 to 79.6)	5.3 (4.2 to 6.7)	99.4 (99.2 to 99.6)	3.4 (3 to 3.9)	0.3 (0.2 to 0.5)
Within 72 hours	NEWS	183	69.7 (51.3 to 84.4)	72.7 (68.9 to 76.3)	12.6 (8.1 to 18.3)	97.7 (95.8 to 98.9)	2.6 (2 to 3.3)	0.4 (0.2 to 0.7)	710	52.7 (43.8 to 61.5)	88.7 (87.9 to 89.6)	9.7 (7.6 to 12.1)	98.8 (98.4 to 99.1)	4.7 (3.9 to 5.6)	0.5 (0.4 to 0.6)
Within 72 hours	NEWS2	300	78.8 (61.1 to 91)	53.3 (49.2 to 57.4)	8.7 (5.7 to 12.4)	97.8 (95.5 to 99.1)	1.7 (1.4 to 2.1)	0.4 (0.2 to 0.8)	1300	73.3 (64.8 to 80.6)	78.9 (77.8 to 79.9)	7.4 (6 to 8.9)	99.2 (98.9 to 99.5)	3.5 (3.1 to 3.9)	0.3 (0.3 to 0.5)

Table S3 Sensitivity analysis of NEWS versus NEWS2 in predicting the risk in-hospital mortality, mortality within 24 hours, 48 hours, and 72 hours at NEWS (or NEWS2)≥5 in the COVID-19 and Non-COVID-19 medical admissions. PPV=Positive Predictive Value; NPV= Negative Predictive Value; LR+=Positive Likelihood Ratio; LR-=Negative Likelihood Ratio; N*= Number of positive cases identified by model at NEWS (or NEWS2)≥5.

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Use of the first National Early Warning Score recorded within 24 hours of admission to estimate the risk of in-hospital mortality in unplanned COVID-19 patients: a retrospective cohort study

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Use of the first National Early Warning Score recorded within 24 hours of admission to estimate the risk of in-hospital mortality in unplanned COVID-19 patients: a retrospective cohort study

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Abstract

Objectives: Although the National Early Warning Score (NEWS) and its latest version NEWS2 are recommended for monitoring for deterioration in patients admitted to hospital, little is known about their performance in COVID-19 patients. We aimed to compare the performance of the NEWS and NEWS2 in patients with COVID-19 versus those without during the first phase of the pandemic.

Design:a retrospective cross-sectional study

Setting: Two acute hospitals (Scarborough and York) are combined into a single dataset and analysed collectively.

Participants: Adult (>=18 years) non-elective admissions discharged between 11-March-2020 to 13-June-2020 with an index or on-admission NEWS2 electronically recorded within ±24 hours of admission are used to predict mortality at four-time points (in-hospital, 24hours, 48hours, and 72hours) in COVID-19 versus non-COVID-19 admissions.

Results: Out of 6480 non-elective admissions, 620 (9.6%) had a diagnosis of COVID-19. They were older (73.3 vs 67.7yrs), more often male (54.7% vs 50.1%), had higher index NEWS (4 vs 2.5) and NEWS2 (4.6 vs 2.8) scores and higher in-hospital mortality (32.1% vs 5.8%). The c-statistics for predicting in-hospital mortality in COVID-19 admissions was significantly lower using NEWS (0.64 vs 0.74) or NEWS2 (0.64 vs 0.74), however these differences reduced at 72hours (NEWS: 0.75 vs 0.81; NEWS2: 0.71 vs 0.81), 48 hours (NEWS: 0.78 vs 0.81; NEWS2: 0.76 vs 0.82) and 24hours (NEWS: 0.84 vs 0.84; NEWS2: 0.86 vs 0.84). Increasing NEWS2 values reflected increased mortality, but for any given value the absolute risk was on average 24% higher (e.g., NEWS2=5: 36% vs 9%).

Conclusions:The index or on-admission NEWS and NEWS2 offer lower discrimination for COVID-19 admissions versus non-COVID-19 admissions. The index NEWS2 is not better than the index NEWS. For each value of the index NEWS or index NEWS2, COVID-19 admissions had a substantially higher risk of mortality than non-COVID-19 admissions which reflects the increased baseline mortality risk of COVID-19.

Keywords: NEWS, NEWS2, COVID-19, mortality risk, early warning scores

Article Summary

- This study data is from a single NHS Trust and used the index NEWS/NEWS2 scores. The extent to which these findings are generalisable, especially to minority ethnic groups with higher mortality, needs further study.
- Although we found no evidence of NEWS2 as having a superior performance to NEWS, this does suggest that the additional enhancements in NEWS2 are having a limited impact and the underlying reasons need further study.
- NEWS and NEWS2 are repeatedly updated for each patient according to local hospital protocols, and the extent to which changes in NEWS or NEWS2 over time reflect changes in mortality risk needs further study.

Introduction

The novel coronavirus SARS-CoV-2, which was declared as a pandemic on 11-March 2020, produces the newly identified disease 'COVID-19' in patients with symptoms (Coronaviridae Study Group of the International Committee on Taxonomy of Viruses[1]) which has challenged health care systems worldwide.

Patients with COVID-19 admitted to a hospital can develop severe disease with life threatening respiratory and/or multi-organ failure [2,3] with a high risk of mortality in part due to the lack of an effective treatment for the underlying disease in the early phase of the pandemic. Thus, it is recommended that patients at risk of deterioration are referred to critical care. The appropriate early assessment and management of patients with COVID-19 is important in ensuring high-quality care.

In the UK National Health Service (NHS), the patient's vital signs are monitored and summarised into a National Early Warning Score (NEWS) or its latest iteration (NEWS2)[4]. NEWS is used across the world [4]. NEWS and NEWS2 are calculated from six physiological variables or vital signs—respiration rate, oxygen saturation, temperature, systolic blood pressure, heart rate and level of consciousness (alert, confusion, voice, pain, unresponsive) and also use of supplemental oxygen—which are routinely collected by nursing staff as an integral part of the process of care, usually for all patients, and then repeated thereafter depending on local hospital protocols. NEWS2 includes two oxygen saturation scales (scale 1 and scale 2) and new confusion[5]. NEWS2 points are allocated according to these clinical observations. A higher NEWS2 correlates with a higher chance of deterioration. Gidari et al. [6] evaluated NEWS2 at hospital admission of patients with COVID-19 as a predictor of ICU admission. Furthermore, Kostakis et al [7] investigated association of the last or ultimate recorded NEWS2/NEWS within 24 hours of death or ICU admission in COVID-19 and non-COVID cohorts.

Although NEWS2 is recommended for clinical use in patients with COVID-19 [8], little is known about how NEWS2 performs in practice. In this study, we aimed to compare the performance of NEWS and NEWS2, in unplanned admissions to a teaching hospital during the first phase of the novel coronavirus SARS CoV-2 (COVID-19) pandemic, in predicting in-hospital mortality at four time points (24hours, 48hours,72hours and in-hospital mortality) in COVID-19 versus non-COVID-19 admissions. For all our analyses we use the on-admission or index NEWS2 because this is an early indicator of the severity of illness.

Methods

Setting & data

Our cohort of unplanned admissions are from two acute hospitals which are approximately 65 kilometres apart in the Yorkshire & Humberside region of England – Scarborough hospital (n~300 beds) and York Hospital (YH) (n~700 beds), managed by York Teaching Hospitals NHS Foundation Trust. For the purposes of this study, the two acute hospitals are combined into a single dataset and analysed collectively. The hospitals have electronic NEWS2 scores and vital signs recording which are routinely collected as part of the patient's process of care.

We considered all adult (age≥18 years) emergency medical admissions (non-elective/unplanned excluding ambulatory care area patients), discharged during 3 months (11 March 2020 to 13 June 2020), with electronic NEWS2 recorded within ±24 hours of admission. For each emergency admission, we obtained a pseudonymised patient identifier, patient's age (years), gender (male/female), ethnicity, body mass index (BMI kg/m^2), discharge status (alive/dead), admission and discharge date and time, diagnoses codes based on the 10th revision of the International Statistical Classification of Diseases (ICD-10) [9] [10], NEWS2 (including its subcomponents respiratory rate, temperature, systolic pressure, pulse rate, oxygen saturation, oxygen supplementation, oxygen scales 1 & 2, and alertness including confusion) [4,5]. The diastolic blood pressure was recorded at the same time as systolic blood pressure. Historically, diastolic blood pressure has always been a routinely collected physiological variable on vital sign charts and is still collected where electronic observations are in place (see Table S1 & S2 in supplementary material). NEWS2 produces integer values that range from 0 (indicating the lowest severity of illness) to 20 (the maximum NEWS2 value possible). The index NEWS2 was defined as the first electronically recorded NEWS2 within ±24 hours of the admission time as vital signs can be collected before admission. We excluded records where the first NEWS2 was not within ±24 hours of admission or was missing/not recorded (see Table 1). Since NEWS2 extends NEWS, we used the same dataset to compare NEWS and NEWS2 especially as NEWS is still in widespread use. The ICD-10 code 'U071' was used to identify records with COVID-19. We searched, primary and secondary ICD-10 codes for 'U071' for identifying COVID-19.

Statistical Modelling

We began with exploratory analyses including line plots that showed the relationship between age, vital signs, NEWS2/NEWS and risk of in-hospital death in COVID-19 and non-COVID-19. We compared the continuous covariates using a two-sample independent t-test (for normal data) or Wilcoxon rank-sum test (for non-normal data). We compared the categorical covariates using a Chi-square proportion test. P-values less than 0.05 were defined as statistically significant.

We determined the discrimination of NEWS and NEWS2 using the concordance or c-statistic which is interpreted as the probability that a deceased patient has a higher risk of death than a randomly chosen non-deceased patient. For a binary outcome (alive/died), the c-statistic is the area under the Receiver Operating Characteristics (ROC) curve [11]. The ROC curve is a plot of the sensitivity, (true positive rate), versus 1-specificity, (false positive rate), for consecutive predicted risks. A c-statistic of 0.5 is no better than tossing a coin, whilst a perfect model has a c-statistic of 1. In general, values less than 0.7 are considered to show poor discrimination, values of 0.7 to 0.8 can be described as reasonable, and values above 0.8 suggest good discrimination[12]. We developed two separate logistic regression models for predicting in-hospital mortality with NEWS and NEWS2 as covariates respectively. We assessed the performance of the index NEWS or index NEWS2 in predicting the mortality at four specified time points - 24hour, 48hour, 72hour and in-hospital in COVID-19 and non-COVID-19 patients using the c-statistic. For each time point we use the index or on-admission NEWS2/NEWS score.

We assessed the sensitivity, specificity, positive predictive value, negative predictive value and likelihood ratios for NEWS and NEWS2 at values ≥5 which is the usual threshold value for escalation to critical care which equates to a 13% mortality risk under NEWS and an 11% risk under NEWS2. The 95% confidence interval for the c-statistic was derived using DeLong's method as implemented in the *pROC* library [13] in R [14]. We followed the STROBE guidelines to report the findings [15]. All analyses were undertaken using *R* [14] and Stata [16].

Ethical Approval

This study used de-identified data and received ethical approval from the Health Research Authority (HRA) and Health and Care Research Wales (HCRW) (reference number 19/HRA/0548).

Patient and Public Involvement:

There was no patient involvement in this study.

Results

Cohort description

There were 6480 discharges over 3 months. We excluded 36 (0.6%) records because the index NEWS2 was not recorded within ±24 hours of the admission date/time or NEWS2 was missing or not recorded at all (see Table S3 in supplementary material).

We analysed data from 6444 admissions, of which 9.6% (620/6444) were diagnosed COVID-19. The demographic, vital signs and outcome profiles of the COVID-19 versus non-COVID-19 admissions is shown in Table 1 and Figure S1. COVID-19 admissions were older (73.3 vs 67.7, p<0.001), more likely to be male (54.7% vs 50.1%, p<0.001), with higher BMI (kg/m2) (27.5 vs 26, p<0.001) than non-COVID-19 admissions. Furthermore, they had higher index NEWS (4.0 vs 2.5, p<0.001) and index NEWS2 (4.6 vs 2.8, p<0.001) than non-COVID-19 admissions which was reflected in differences in vital signs notably, a higher respiratory rate (23.5 vs 19.8, p<0.001), lower oxygen saturation (94.8% vs 96.4%, p<0.001), higher frequency of oxygen supplementation (33.4% vs 11.5%, p<0.001), lower systolic blood pressure (136.1 mmHg vs 142.5 mm Hg, p<0.001) and less likely to be alert (82.9% vs 90%, p<0.001).

COVID-19 admissions were more likely to be referred to the critical outreach team (14.7% vs 3.6%, p<0.001), admitted to the intensive care unit (ICU) (6.8% vs 2.5%) and referred to palliative care (10.5% vs 4.9%). They also had longer hospital stay (7.3 days vs 3.0 days, p<0.001) and higher in-hospital mortality (32.1% vs 5.8%, p<0.001).

Figure 1 shows the relationship between continuous covariates and the observed risk of in-hospital mortality in COVID-19 versus non-COVID-19 admissions. Whilst the pattern of mortality was broadly similar between COVID-19 and non-COVID-19 admissions, COVID-19 admissions had a consistently higher risk of mortality for the range of covariate values (see Figure 1 and Figure S2 in supplementary material). Figure 1 also shows that although increasing NEWS and NEWS2 scores reflected increased mortality, but for any given value of NEWS or NEWS2 the risk of mortality for COVID-19 was on average 24% higher and at a NEWS or NEWS2 of 5 the risk of mortality in COVID-19 vs Non-COVID-19 was 36% versus 9%.

The performance of index NEWS2 to predict the risk of death (24hour, 48hour, 72hour, in-hospital) in COVID-19 and non-COVID-19 admissions is shown in Figure 2 and Table S4. The c-statistics for predicting in-hospital mortality in COVID-19 admissions was significant lower than for patients without COVID-19 (NEWS: 0.64 vs 0.74; NEWS2: 0.64 vs 0.74), however these differences reduced at 72hours (NEWS: 0.75 vs 0.81; NEWS2: 0.71 vs 0.81), 48 hours (NEWS: 0.78 vs 0.81; NEWS2: 0.76 vs 0.82) and

24hours (NEWS: 0.84 vs 0.84; NEWS2: 0.86 vs 0.84). We found the same performance for medical and surgical admission (see Table S5 in supplementary material).

Table 2 includes the sensitivity, specificity, positive and negative predictive values for NEWS and NEWS2 for COVID-19 and non-COVID-19 patients. NEWS2 had higher sensitivity but lower specificity compared to NEWS.

Characteristic	COVID-19	Non-COVID-19	p-value
N	620	5824	-
Male (%)	339 (54.7)	2918 (50.1)	0.033
Mean Age [years] (SD)	73.3 (15.4)	67.7 (19)	<0.001
Admission type			<0.001
Medical	588 (94.8)	4727 (81.1)	
Surgical	32 (5.2)	1097 (18.9)	
Ethnicity			<0.001
White	465 (75)	4668 (80.2)	
Black, Asian, and other minority ethnic	34 (5.5)	152 (2.6)	
Missing	121 (19.5)	1004 (17.2)	
Median BMI (IQR)* [kg/m^2]	27.5 (8.4)	26 (7.6)	<0.001
Mean NEWS (SD)	4 (2.8)	2.5 (2.3)	<0.001
Mean NEWS2 (SD)	4.6 (3)	2.8 (2.7)	<0.001
Vital Signs			
Mean Respiratory rate [breaths per minute] (SD)	23.5 (6.6)	19.8 (5)	<0.001
Mean Temperature [oC] (SD)	36.8 (1.1)	36.3 (0.9)	<0.001
Mean Systolic pressure [mmHg] (SD)	136.1 (25.8)	142.5 (29.2)	<0.001
Mean Diastolic pressure [mmHg] (SD)	76.5 (16.3)	79.4 (16.8)	<0.001
Mean Pulse rate [beats per minute] (SD)	92.2 (22.1)	88.5 (22.2)	<0.001
Mean % Oxygen saturation (SD)	94.8 (4.4)	96.4 (2.9)	<0.001
Oxygen supplementation (%)	207 (33.4)	667 (11.5)	<0.001
Mean oxygen flow rate [Litre per minute] (SD)	7.6 (5.8)	6.4 (5.5)	0.008
Oxygen scale 2 (%)	42 (6.8)	361 (6.2)	0.634
Alertness			<0.001
Alert (%)	514 (82.9)	5239 (90)	
Baseline confusion (%)	5 (0.8)	45 (0.8)	
New confusion (%)	19 (3.1)	82 (1.4)	
Pain (%)	0 (0)	49 (0.8)	
Voice (%)	58 (9.4)	227 (3.9)	
Unconscious (%)	24 (3.9)	182 (3.1)	
Referred to critical outreach team (%)	91 (14.7)	211 (3.6)	<0.001
Admission to ICU (%)	42 (6.8)	147 (2.5)	<0.001
Palliative care (%)	65 (10.5)	288 (4.9)	<0.001
On ventilation (%)	18 (2.9)	12 (0.2)	<0.001
Median Length of Stay (days) (IQR)	7.3 (11.7)	3 (5.5)	<0.001
Mortality with-in 24 hours (%)	9 (1.5)	53 (0.9)	0.273
Mortality with-in 48 hours (%)	15 (2.4)	94 (1.6)	0.189

Mortality with-in 72 hours (%)	33 (5.3)	131 (2.3)	<0.001
In-hospital Mortality	199 (32.1)	336 (5.8)	<0.001

Table 1 Characteristics of emergency medical admissions in COVID-19 versus non-COVID-19

** BMI is missing 188 (30.3%) for COVID and 2283 (39.2%) for Non-COVID*

Mortality type	Models	COVID-19							Non-COVID-19						
		N*	Sensitivity%	Specificity%	PPV	NPV	LR+	LR-	N*	Sensitivity%	Specificity%	PPV	NPV	LR+	LR-
In-hospital	NEWS	183	45.7 (38.7 to 52.9)	78.1 (73.9 to 82)	49.7 (42.3 to 57.2)	75.3 (71 to 79.3)	2.1 (1.7 to 2.6)	0.7 (0.6 to 0.8)	710	40.8 (35.5 to 46.2)	89.6 (88.7 to 90.4)	19.3 (16.5 to 22.4)	96.1 (95.5 to 96.6)	3.9 (3.4 to 4.5)	0.7 (0.6 to 0.7)
In-hospital	NEWS2	300	62.8 (55.7 to 69.5)	58.4 (53.6 to 63.2)	41.7 (36 to 47.5)	76.9 (71.9 to 81.4)	1.5 (1.3 to 1.8)	0.6 (0.5 to 0.8)	1300	59.2 (53.8 to 64.5)	79.9 (78.9 to 81)	15.3 (13.4 to 17.4)	97 (96.4 to 97.5)	3 (2.7 to 3.3)	0.5 (0.4 to 0.6)
Within 24 hours	NEWS	183	88.9 (51.8 to 99.7)	71.4 (67.6 to 74.9)	4.4 (1.9 to 8.4)	99.8 (98.7 to 100)	3.1 (2.4 to 4)	0.2 (0 to 1)	710	60.4 (46 to 73.5)	88.3 (87.4 to 89.1)	4.5 (3.1 to 6.3)	99.6 (99.4 to 99.7)	5.1 (4.1 to 6.5)	0.4 (0.3 to 0.6)
Within 24 hours	NEWS2	300	88.9 (51.8 to 99.7)	52.2 (48.2 to 56.2)	2.7 (1.2 to 5.2)	99.7 (98.3 to 100)	1.9 (1.5 to 2.4)	0.2 (0 to 1.4)	1300	77.4 (63.8 to 87.7)	78.2 (77.1 to 79.2)	3.2 (2.3 to 4.3)	99.7 (99.5 to 99.9)	3.5 (3 to 4.1)	0.3 (0.2 to 0.5)
Within 48 hours	NEWS	183	80 (51.9 to 95.7)	71.7 (68 to 75.3)	6.6 (3.4 to 11.2)	99.3 (98 to 99.9)	2.8 (2.1 to 3.8)	0.3 (0.1 to 0.8)	710	54.3 (43.7 to 64.6)	88.5 (87.6 to 89.3)	7.2 (5.4 to 9.3)	99.2 (98.9 to 99.4)	4.7 (3.9 to 5.8)	0.5 (0.4 to 0.6)
Within 48 hours	NEWS2	300	86.7 (59.5 to 98.3)	52.6 (48.5 to 56.6)	4.3 (2.3 to 7.3)	99.4 (97.8 to 99.9)	1.8 (1.5 to 2.3)	0.3 (0.1 to 0.9)	1300	73.4 (63.3 to 82)	78.5 (77.4 to 79.6)	5.3 (4.2 to 6.7)	99.4 (99.2 to 99.6)	3.4 (3 to 3.9)	0.3 (0.2 to 0.5)
Within 72 hours	NEWS	183	69.7 (51.3 to 84.4)	72.7 (68.9 to 76.3)	12.6 (8.1 to 18.3)	97.7 (95.8 to 98.9)	2.6 (2 to 3.3)	0.4 (0.2 to 0.7)	710	52.7 (43.8 to 61.5)	88.7 (87.9 to 89.6)	9.7 (7.6 to 12.1)	98.8 (98.4 to 99.1)	4.7 (3.9 to 5.6)	0.5 (0.4 to 0.6)
Within 72 hours	NEWS2	300	78.8 (61.1 to 91)	53.3 (49.2 to 57.4)	8.7 (5.7 to 12.4)	97.8 (95.5 to 99.1)	1.7 (1.4 to 2.1)	0.4 (0.2 to 0.8)	1300	73.3 (64.8 to 80.6)	78.9 (77.8 to 79.9)	7.4 (6 to 8.9)	99.2 (98.9 to 99.5)	3.5 (3.1 to 3.9)	0.3 (0.3 to 0.5)

Table 2 Sensitivity analysis of NEWS versus NEWS2 in predicting the risk in-hospital mortality, mortality within 24 hours, 48 hours, and 72 hours at NEWS (or NEWS2)≥5 in the COVID-19 and Non-COVID-19 medical admissions. PPV=Positive Predictive Value; NPV= Negative Predictive Value; LR+=Positive Likelihood Ratio; LR-=Negative Likelihood Ratio; N*= Number of positive cases identified by model at NEWS (or NEWS2)≥5.

Discussion

Whilst NEWS and NEWS2 are recommended for monitoring patients with COVID-19, we found that the index or on-admission NEWS2/NEWS offer lower discrimination for COVID-19 patients versus non-COVID-19 patients. We also found that the index NEWS2 was not better than index NEWS. For each value of the index NEWS2/NEWS, COVID-19 patients had a substantially higher risk of in-hospital mortality than non-COVID-19 patients, which equated to an average 24% risk difference which reflects the higher baseline risk of mortality in our COVID-19 patients. However, the c-statistics for the index NEWS2/NEWS2 improved with shorter time horizons with the highest discrimination (above 0.8) being seen for predicting mortality risk within 24hours of the index NEWS2/NEWS.

A recent paper by Kostakis et al [7], found good discrimination for NEWS or NEWS2 (c-statistics 0.842-0.894) concluding that their "results support the national and international recommendations for the use of NEWS or NEWS2 for the assessment of acute-illness severity in patients with COVID-19." In contrast to our approach, Kostakis et al [7] used the last or ultimate recorded NEWS2/NEWS within 24 hours of death or ICU admission. We note that when we consider death within 24 hours of admission, our reported c-statistics for index NEWS2/NEWS are comparable with those of Kostakis et al [7].

So taken together these findings indicate that care must be taken not to interpret the predictive power of the ultimate NEWS or NEWS2 score (taken within 24 hours of death) as being equivalent to the predictive power of the index NEWS of NEWS2 score (or preceding NEWS or NEWS2 scores) for risk of in-hospital mortality. The ultimate NEWS or NEWS2 is an accurate predictor of mortality (plus ICU admission in the case of Kostakis et al) for COVID-19 patients but offers a maximum of 24hours for appropriate interventions. This good performance is less surprising when we note that, with the exception of patients who are characterised by abnormal physiology (patients recovering from end-stage renal failure or patients recovering from brain injury), "Patients die not from their disease but from the disordered physiology caused by the disease." [17]. But, as our findings show, the performance of the index NEWS or index NEWS2 for predicting death in hospital, which offers an early window of opportunity for assessment and intervention, is poorer especially for COVID-19 patients. This needs to be brought to the attention of medical and nursing staff and reflected in escalation protocols and guidelines (which have always highlighted the importance of clinical judgement) to mitigate potential threats to patient safety by promoting situational awareness about the actual, on admission, in-hospital mortality risk for COVID-19 patients.

The World Health Organisation (WHO) describes the range of symptoms seen in COVID-19 which include (but are not limited to) dyspnoea, reduced alertness, delirium, fever, tachypnoea and hypoxia

(as a common sign in moderate to severe disease). These symptoms are included in the physiological observation set underpinning NEWS and NEWS2 and were more frequent in our COVID-19 patients compared to non-COVID-19 patients. We also found evidence of lower blood pressure and a higher pulse rate in COVID-19 patients. The NEWS2 guidelines[8] do note that patients with COVID-19 can develop 'silent hypoxia' where oxygen saturations can drop to low levels and precipitate acute respiratory failure quickly without the presence of obvious symptoms of respiratory distress. As such any patients admitted and on supplemental oxygen may develop a rapidly increasing oxygen requirement that may not increase the NEWS2 score. It is stressed that any increase in oxygen requirement should trigger an escalation for review by a competent senior decision-maker [8].

Consideration should be also be given to enhancing NEWS or NEWS2 so that they can be used in COVID-19 and non-COVID-19 patients rather than needing to change scoring systems or adjust estimations of risk dependent on diagnosis. We have previously demonstrated how a fully automated computer-enhanced NEWS score can be developed which requires no additional data collection and builds on the standardisation provided by NEWS [18]. We now propose to extend this to include COVID-19 status.

There are several limitations to our study. (1) This study data is from a single NHS Trust and the extent to which these findings are generalisable, especially to minority ethnic groups with higher COVID-19 mortality, needs further study. (2) We used the index NEWS2 which reflects the 'on-admission' risk of mortality of the patients. Nonetheless, NEWS2 is repeatedly updated for each patient according to local hospital protocols, and the extent to which changes in NEWS2 over time reflect changes in mortality risk needs further study. (3) Although we found no evidence of NEWS2 as having a superior performance to NEWS, it is important to note that our index NEWS data are hypothetical in the sense that the Trust has been using NEWS2 since April 2019. Nevertheless, it is worth noting that a recent, albeit small Italian study based on 71 hospitalised COVID-19 patients found NEWS2 to be a good predictor (with a high c-statistic 0.90) of subsequent ICU admission for COVID-19 patients but was not able to consider mortality because of insufficient events [6]. Our study did not consider ICU admissions as an outcome because the number of ICU admissions were low but Kostakis et al [7] used it as a composite outcome with in-hospital mortality (5).

Conclusions

The index or on-admission NEWS and NEWS2 offer lower discrimination for COVID-19 admissions versus non-COVID-19 admissions. The index NEWS2 is not better than the index NEWS. For each value

of the index NEWS or index NEWS2, COVID-19 admissions had a substantially higher risk of mortality than non-COVID-19 admissions which reflects the increased baseline mortality risk of COVID-19.

Contributorship

DR & MAM had the original idea for this work. MF undertook the statistical analyses with guidance from MAM. MFi & KB extracted the necessary data frames. DR gave a clinical perspective. DR, MF and MAM wrote the first draft of this paper and all authors subsequently assisted in redrafting and have approved the final version.

Competing Interests

The authors declare no conflicts of interest.

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Data Availability Statement

Our data sharing agreement with NHS York hospital trust does not permit us to share this data with other parties. Nonetheless if anyone is interested in the data, then they should contact the R&D offices in the first instance.

Figure 1 Line plots showing the observed risk of in-hospital mortality with continuous covariates for COVID-19 (black colour) and Non-COVID-19 (grey colour) admissions.

Note: Size of circles reflects sample size independently in the COVID-19 and non-COVID-19 groups.

Figure 2 Receiver Operating Characteristic curve for NEWS2 and NEWS in predicting the risk of in-hospital mortality, mortality within 24 hours, 48 hours, and 72 hours in the COVID-19 (black colour) and Non-COVID-19 (grey colour) admissions.

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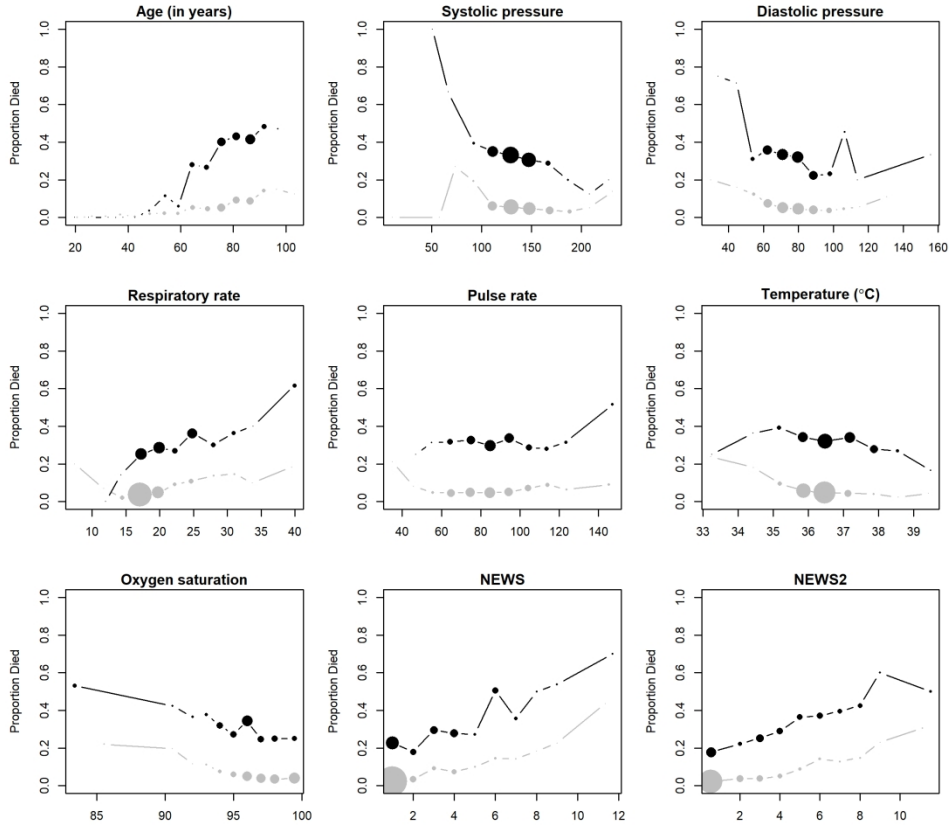
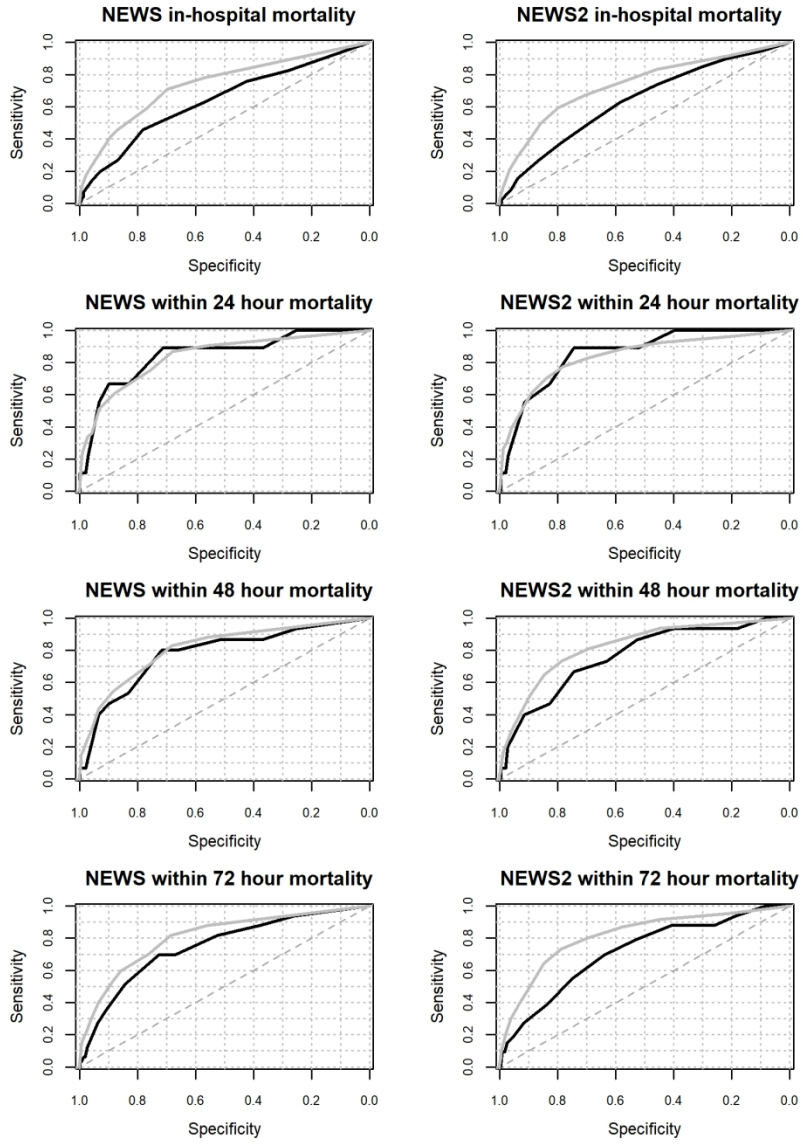


Line plots showing the observed risk of in-hospital mortality with continuous covariates for COVID-19 (black colour) and Non-COVID-19 (grey colour) admissions.
Note: Size of circles reflects sample size independently in the COVID-19 and non-COVID-19 groups.

228x203mm (300 x 300 DPI)



Receiver Operating Characteristic curve for NEWS2 and NEWS in predicting the risk of in-hospital mortality, mortality within 24 hours, 48 hours, and 72 hours in the COVID-19 (black colour) and Non-COVID-19 (grey colour) admissions.

152x203mm (300 x 300 DPI)

Table S1: NEWS scoring chart

Physiological Parameters	3	2	1	0	1	2	3
Respiration Rate	≤8		9 - 11	12 - 20		21 - 24	≥25
Oxygen Saturations	≤91	92 - 93	94 - 95	≥96			
Any Supplemental Oxygen		Yes		No			
Temperature	≤35.0		35.1 - 36.0	36.1 - 38.0	38.1 - 39.0	≥39.1	
Systolic BP	≤90	91 - 100	101 - 110	111 - 219			≥220
Heart Rate	≤40		41 - 50	51-90	91 - 110	111 - 130	≥131
Level of Consciousness				Alert			Voice, Pain, or Unconscious

Table S2: NEWS2 scoring chart

Physiological Parameters	3	2	1	0	1	2	3
Respiration Rate	≤8		9 - 11	12 - 20		21 - 24	≥25
SpO2 Scale 1 (%)	≤91	92 - 93	94 - 95	≥96			
SpO2 Scale 2 (%)	≤83	84 - 85	86 - 87	88 - 92 ≥93 on Air	93 – 94 on oxygen	95 – 96 on oxygen	≥97 on oxygen
Oxygen Saturations	≤91	92 - 93	94 - 95	≥96			
Air or oxygen?		Oxygen		Air			
Temperature	≤35.0		35.1 - 36.0	36.1 - 38.0	38.1 - 39.0	≥39.1	
Systolic BP	≤90	91 - 100	101 - 110	111 - 219			≥220
Heart Rate	≤40		41 - 50	51-90	91 - 110	111 - 130	≥131
Level of Consciousness				Alert			Voice, Pain, Confusion, or Unconscious

The NEWS [https://www.rcplondon.ac.uk/projects/outputs/national-early-warning-score-news] is based on a scoring system in which a score is allocated to vital signs physiological measurements already undertaken when patients present to or are being monitored in hospital. A score is allocated to each as they are measured, the magnitude of the score reflecting how extreme the parameter varies from the norm. This score is then aggregated, and uplifted for people requiring oxygen.

Table S3 Number of emergency medical admissions included/excluded

Characteristic	COVID-19	Non-COVID-19	All
	N (%)	N (%)	N (%)
Total emergency medical discharges between 11 Mar 20 to 13 June 20	622 (9.6%)	5858 (90.4%)	6480 (100%)
Excluded: No NEWS recorded (%)	0 (0.0)	19 (0.3)	19 (0.3)
Excluded: First NEWS after 24 hours of admission (%)	2 (0.3)	15 (0.3)	17 (0.3)
Total excluded (%)	2 (0.3)	34 (0.6)	36 (0.6)
Total included (%)	620 (99.7)	5824 (99.4)	6444 (99.4)

Mortality timepoint		COVID-19				Non-COVID-19			
	Model	Risk discharged alive	Risk discharged deceased	Risk Difference	AUC (95% CI)	Risk discharged alive	Risk discharged deceased	Risk Difference	AUC (95% CI)
In-hospital Mortality	NEWS	0.11	0.16	0.06	0.64 (0.59 to 0.69)	0.07	0.17	0.09	0.74 (0.71 to 0.77)
	NEWS2	0.11	0.15	0.04	0.64 (0.59 to 0.68)	0.07	0.16	0.09	0.74 (0.71 to 0.77)
Mortality with-in 24 hours	NEWS	0.12	0.32	0.20	0.84 (0.7 to 0.99)	0.08	0.25	0.17	0.84 (0.78 to 0.89)
	NEWS2	0.12	0.28	0.16	0.86 (0.75 to 0.97)	0.08	0.24	0.16	0.84 (0.78 to 0.9)
Mortality with-in 48 hours	NEWS	0.12	0.26	0.14	0.78 (0.65 to 0.91)	0.08	0.22	0.14	0.81 (0.77 to 0.86)
	NEWS2	0.12	0.23	0.11	0.76 (0.64 to 0.89)	0.08	0.21	0.14	0.82 (0.78 to 0.87)
Mortality with-in 72 hours	NEWS	0.12	0.23	0.11	0.75 (0.66 to 0.84)	0.08	0.214	0.13	0.81 (0.77 to 0.85)
	NEWS2	0.12	0.21	0.09	0.71 (0.62 to 0.8)	0.08	0.21	0.13	0.82 (0.78 to 0.85)

Table S4 Area under the Receiver Operating Characteristic curve in predicting mortality (in-hospital, 24hour, 48hour, 72hour) at index NEWS2 (or NEWS) ≥ 5 in COVID-19 and Non-COVID-19 emergency medical admissions

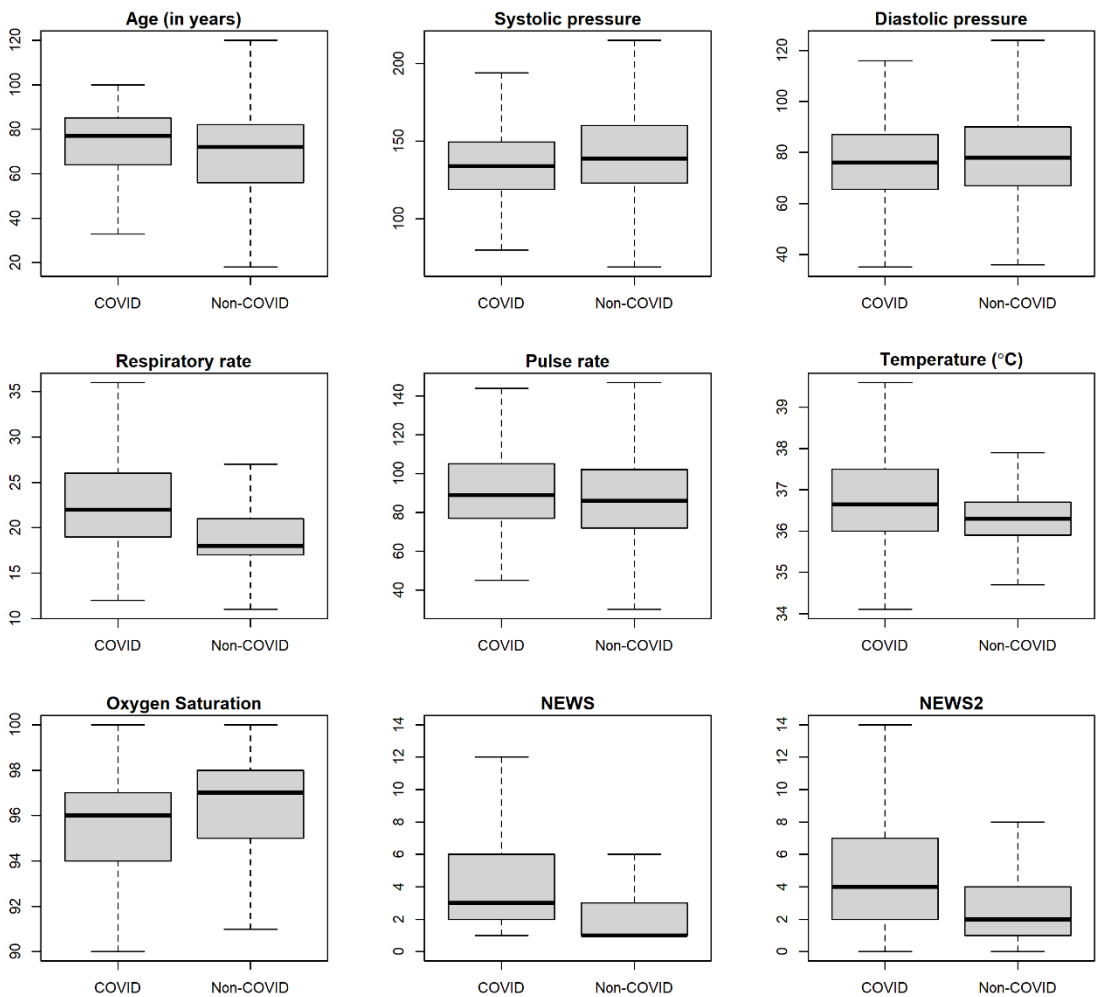


Figure S1 Boxplots without outliers for continuous covariates for COVID-19 versus Non-COVID-19 admissions

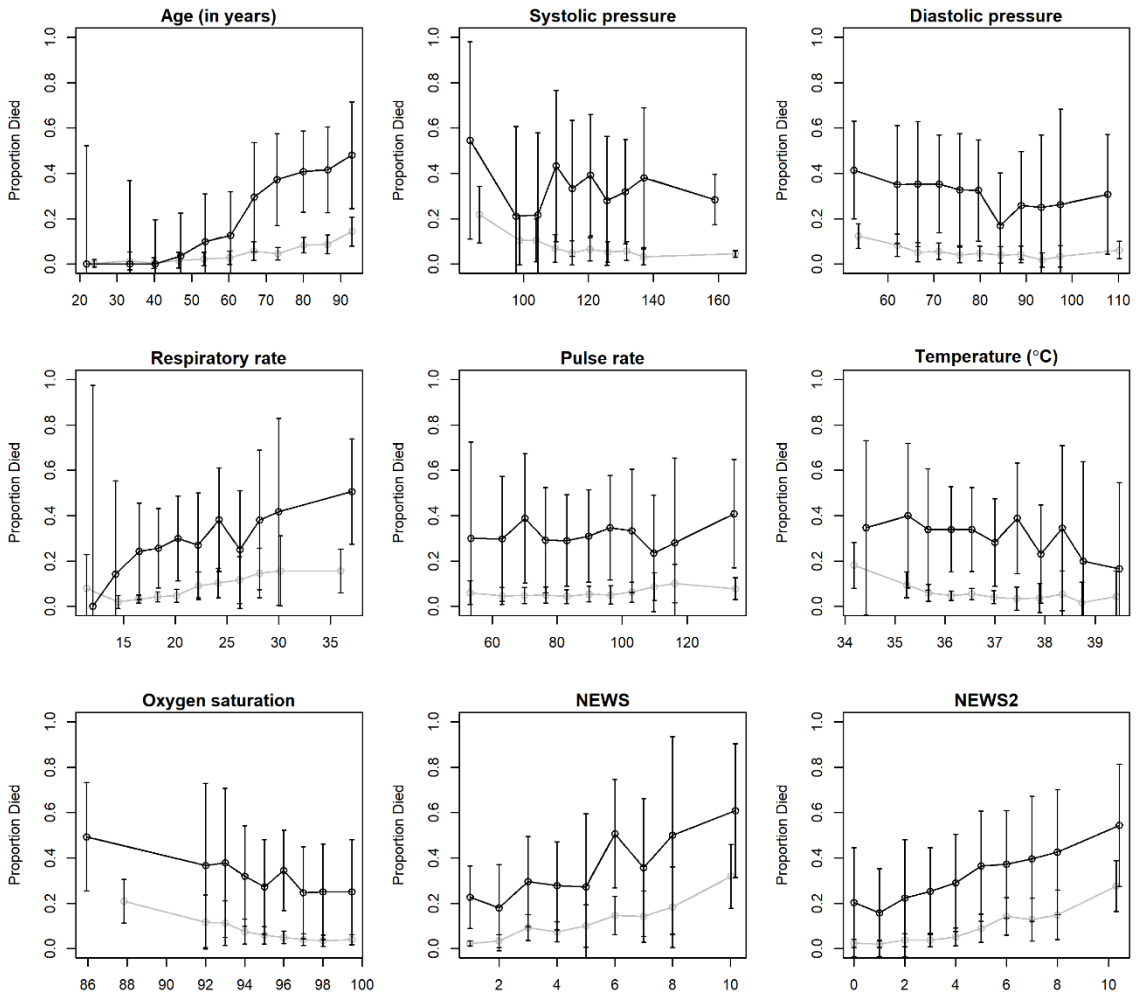


Figure S2 Line plots showing the observed risk of in-hospital mortality (95% confidence intervals) with continuous covariates for COVID-19 versus Non-COVID-19 admissions

Admission type	Medical N= 5313		Surgical N=1129		Both N=6444	
	COVID+	COVID-	COVID+	COVID-	COVID+	COVID-
Number of admission (N)	588	4727	32	1097	620	5824
AUC (95% CI) for NEWS	0.64 (0.60 -0.69)	0.74 (0.71 -0.77)	0.63 (0.43 -0.83)	0.71 (0.63 -0.80)	0.64 (0.60 -0.69)	0.74 (0.71 -0.77)
AUC (95% CI) for NEWS 2	0.64 (0.60 -0.69)	0.73 (0.70 -0.77)	0.65 (0.46 -0.85)	0.74 (0.65 -0.82)	0.64 (0.60 -0.69)	0.74 (0.71 -0.77)

Table S5: Performance of NEWS and NEWS in predicting the in-hospital mortality in medical and surgical admission.

COVID+ = COVID-19 admissions; COVID- = Non-COVID-19 admissions

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **p1,2**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **p2**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **p4**
Objectives	3	State specific objectives, including any prespecified hypotheses **p4**
Methods		
Study design	4	Present key elements of study design early in the paper **p5**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **p5**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants **p5**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **p5**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **p5**
Bias	9	Describe any efforts to address potential sources of bias **p5**
Study size	10	Explain how the study size was arrived at **p5**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **p5**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **p6**
		(*b*) Describe any methods used to examine subgroups and interactions **p6**
		(*c*) Explain how missing data were addressed **p6**
		(*d*) If applicable, describe analytical methods taking account of sampling strategy **p6**
		(*e*) Describe any sensitivity analyses **p6**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **p7**, **appendix Table S3**
		(b) Give reasons for non-participation at each stage **p7**, **appendix Table S3**
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **p7,8**
		(b) Indicate number of participants with missing data for each variable of interest **p6**, **appendix Table S3**
Outcome data	15*	Report numbers of outcome events or summary measures **p7,8**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **p7,8**
		(*b*) Report category boundaries when continuous variables were categorized

		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **p7,8**
Discussion		
Key results	18	Summarise key results with reference to study objectives **p11**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **p11**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **p11**
Generalisability	21	Discuss the generalisability (external validity) of the study results **p11,12**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **p13**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Use of the first National Early Warning Score recorded within 24 hours of admission to estimate the risk of in-hospital mortality in unplanned COVID-19 patients: a retrospective cohort study

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Use of the first National Early Warning Score recorded within 24 hours of admission to estimate the risk of in-hospital mortality in unplanned COVID-19 patients: a retrospective cohort study

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Abstract

Objectives: Although the National Early Warning Score (NEWS) and its latest version NEWS2 are recommended for monitoring deterioration in patients admitted to hospital, little is known about their performance in COVID-19 patients. We aimed to compare the performance of the NEWS and NEWS2 in patients with COVID-19 versus those without during the first phase of the pandemic.

Design:A retrospective cross-sectional study

Setting: Two acute hospitals (Scarborough and York) are combined into a single dataset and analysed collectively.

Participants: Adult (≥18 years) non-elective admissions discharged between 11-March-2020 to 13-June-2020 with an index or on-admission NEWS2 electronically recorded within ±24 hours of admission to predict mortality at four-time points (in-hospital, 24hours, 48hours, and 72hours) in COVID-19 versus non-COVID-19 admissions.

Results: Out of 6480 non-elective admissions, 620 (9.6%) had a diagnosis of COVID-19. They were older (73.3 vs 67.7yrs), more often male (54.7% vs 50.1%), had higher index NEWS (4 vs 2.5) and NEWS2 (4.6 vs 2.8) scores and higher in-hospital mortality (32.1% vs 5.8%). The c-statistics for predicting in-hospital mortality in COVID-19 admissions was significantly lower using NEWS (0.64 vs 0.74) or NEWS2 (0.64 vs 0.74), however these differences reduced at 72hours (NEWS: 0.75 vs 0.81; NEWS2: 0.71 vs 0.81), 48 hours (NEWS: 0.78 vs 0.81; NEWS2: 0.76 vs 0.82) and 24hours (NEWS: 0.84 vs 0.84; NEWS2: 0.86 vs 0.84). Increasing NEWS2 values reflected increased mortality, but for any given value the absolute risk was on average 24% higher (e.g., NEWS2=5: 36% vs 9%).

Conclusions:The index or on-admission NEWS and NEWS2 offers lower discrimination for COVID-19 admissions versus non-COVID-19 admissions. The index NEWS2 was not proven to be better than the index NEWS. For each value of the index NEWS/NEWS2, COVID-19 admissions had a substantially higher risk of mortality than non-COVID-19 admissions which reflects the increased baseline mortality risk of COVID-19.

Keywords: NEWS, NEWS2, COVID-19, mortality risk, early warning scores

Article Summary

- This study data is from a single NHS Trust and used the index NEWS/NEWS2 scores. The extent to which these findings are generalisable, especially to minority ethnic groups with higher mortality, require further study.
- Although we found no evidence of NEWS2 as having a superior performance to NEWS, this does suggest that the additional enhancements in NEWS2 are having a limited impact and the underlying reasons need further study.
- NEWS and NEWS2 are repeatedly updated for each patient according to local hospital protocols, and the extent to which changes in NEWS or NEWS2 over time reflect changes in mortality risk needs further study.

Introduction

The novel coronavirus SARS-CoV-2, which was declared as a pandemic on 11-March 2020, produces the newly identified disease 'COVID-19' in patients with symptoms (Coronaviridae Study Group of the International Committee on Taxonomy of Viruses[1]) which has challenged health care systems worldwide.

Patients with COVID-19 admitted to hospital can develop severe disease with life threatening respiratory and/or multi-organ failure [2,3] with a high risk of mortality in part due to the lack of effective treatment for the underlying disease in the early phase of the pandemic. Thus, it is recommended that patients at risk of deterioration are referred to critical care. The appropriate early assessment and management of patients with COVID-19 is important in ensuring high-quality care.

In the UK National Health Service (NHS), the patient's vital signs are monitored and summarised into a National Early Warning Score (NEWS) or its latest iteration, NEWS2 [4]. NEWS is used across the world [4]. NEWS and NEWS2 are calculated from six physiological variables or vital signs—respiration rate, oxygen saturation, temperature, systolic blood pressure, heart rate and level of consciousness (alert, confusion, voice, pain, unresponsive) and also use of supplemental oxygen—routinely collected by nursing staff as an integral part of the process of care, usually for all patients, and then repeated thereafter depending on local hospital protocols. NEWS2 includes two oxygen saturation scales (scale 1 and scale 2) and new confusion[5]. NEWS2 points are allocated according to these clinical observations. A higher NEWS2 correlates with a higher chance of deterioration. Gidari et al. [6] evaluated NEWS2 at hospital admission of patients with COVID-19 as a predictor of ICU admission. Furthermore, Kostakis et al [7] investigated association of the last or ultimate recorded NEWS2/NEWS within 24 hours of death or ICU admission in COVID-19 and non-COVID cohorts.

Although NEWS2 is recommended for clinical use in patients with COVID-19 [8], little is known about how NEWS2 performs in practice. In this study, we aimed to compare the performance of NEWS and NEWS2 via unplanned admissions to a teaching hospital during the first phase of the novel coronavirus SARS CoV-2 (COVID-19) pandemic, in predicting in-hospital mortality at four time points (24hours, 48hours,72hours and in-hospital mortality) in COVID-19 versus non-COVID-19 admissions. For all our analyses we use the on-admission or index NEWS2/NEWS because this is an early indicator of the severity of illness.

Methods

Setting and Data

Our cohort of unplanned admissions are from two acute hospitals which are approximately 65 kilometres apart in the Yorkshire and the Humber region of England – Scarborough hospital (n~300 beds) and York Hospital (YH) (n~700 beds), managed by York Teaching Hospitals NHS Foundation Trust. For the purposes of this study, the two acute hospitals are combined into a single dataset and analysed collectively. The hospitals have electronic NEWS2 scores and vital signs recording which are routinely collected as part of the patient's process of care.

We considered all adult (age≥18 years) emergency medical admissions (non-elective/unplanned excluding ambulatory care area patients), discharged during 3 months (11 March 2020 to 13 June 2020), with electronic NEWS2 recorded within ±24 hours of admission. For each emergency admission, we obtained a pseudonymised patient identifier, patient's age (years), sex (male/female), ethnicity, body mass index (BMI kg/m^2), discharge status (alive/dead), admission and discharge date and time, diagnoses codes based on the 10th revision of the International Statistical Classification of Diseases (ICD-10) [9] [10], NEWS2 (including its subcomponents respiratory rate, temperature, systolic pressure, pulse rate, oxygen saturation, oxygen supplementation, oxygen scales 1 & 2, and alertness including confusion) [4,5]. The diastolic blood pressure was recorded at the same time as systolic blood pressure. Historically, diastolic blood pressure has always been a routinely collected physiological variable on vital sign charts and is still collected where electronic observations are in place (see Table S1 & S2 in supplementary material). NEWS2 produces integer values that range from 0 (indicating the lowest severity of illness) to 20 (the maximum NEWS2 value possible). The index NEWS2 was defined as the first electronically recorded NEWS2 within ±24 hours of the admission time as vital signs can be collected before admission. We excluded records where the first NEWS2 was not within ±24 hours of admission or was missing/not recorded (see Table 1). Since NEWS2 extends NEWS, we used the same dataset to compare NEWS and NEWS2 especially as NEWS is still in widespread use. The ICD-10 code 'U071' was used to identify records with COVID-19. We searched, primary and secondary ICD-10 codes for 'U071' for identifying COVID-19.

Statistical Modelling

We began with exploratory analyses including line plots that showed the relationship between age, vital signs, NEWS2/NEWS and risk of in-hospital death in COVID-19 and non-COVID-19. We compared the continuous covariates using a two-sample independent t-test (for normal data) or Wilcoxon rank-sum test (for non-normal data). We compared the categorical covariates using a Chi-square proportion test. P-values less than 0.05 were defined as statistically significant.

We determined the discrimination of NEWS and NEWS2 using the concordance or c-statistic which is interpreted as the probability that a deceased patient had a higher risk of death than a randomly chosen non-deceased patient. For a binary outcome (alive/died), the c-statistic is the area under the Receiver Operating Characteristics (ROC) curve [11]. The ROC curve is a plot of the sensitivity, (true positive rate), versus 1-specificity, (false positive rate), for consecutive predicted risks. A c-statistic of 0.5 is no better than tossing a coin, whilst a perfect model has a c-statistic of 1. In general, values less than 0.7 are considered to show poor discrimination, values of 0.7 to 0.8 can be described as reasonable, and values above 0.8 suggest good discrimination[12]. We developed two separate logistic regression models for predicting in-hospital mortality with NEWS and NEWS2 as covariates respectively. We assessed the performance of the index NEWS or index NEWS2 in predicting the mortality at four specified time points - 24hour, 48hour, 72hour and in-hospital in COVID-19 and non-COVID-19 patients using the c-statistic. For each time point we used the index or on-admission NEWS2/NEWS score.

We assessed the sensitivity, specificity, positive predictive value, negative predictive value and likelihood ratios for NEWS and NEWS2 at values ≥5 which is the usual threshold value for escalation to critical care which equates to a 13% mortality risk under NEWS and an 11% risk under NEWS2. The 95% confidence interval for the c-statistic was derived using DeLong's method as implemented in the *pROC* library [13] in R [14]. We followed the STROBE guidelines to report the findings [15]. All analyses were undertaken using *R* [14] and Stata [16].

Ethical Approval

This study used anonymised data and received ethical approval from the Health Research Authority (HRA) and Health and Care Research Wales (HCRW) (reference number 19/HRA/0548).

Patient and Public Involvement:

There was no patient involvement in this study.

Results

Cohort description

There were 6480 discharges over 3 months. We excluded 36 (0.6%) records because the index NEWS2 was not recorded within ±24 hours of the admission date/time or NEWS2 was missing or not recorded at all (see Table S3 in supplementary material).

We analysed data from 6444 admissions, of which 9.6% (620/6444) were diagnosed COVID-19. The demographic, vital signs and outcome profiles of the COVID-19 versus non-COVID-19 admissions is shown in Table 1 and Figure S1. COVID-19 admissions were older (73.3 vs 67.7, p<0.001), more likely to be male (54.7% vs 50.1%, p<0.001), with higher BMI (kg/m2) (27.5 vs 26, p<0.001) than non-COVID-19 admissions. Furthermore, they had higher index NEWS (4.0 vs 2.5, p<0.001) and index NEWS2 (4.6 vs 2.8, p<0.001) than non-COVID-19 admissions which was reflected in differences in vital signs notably, a higher respiratory rate (23.5 vs 19.8, p<0.001), lower oxygen saturation (94.8% vs 96.4%, p<0.001), higher frequency of oxygen supplementation (33.4% vs 11.5%, p<0.001), lower systolic blood pressure (136.1 mmHg vs 142.5 mm Hg, p<0.001) and less likely to be alert (82.9% vs 90%, p<0.001).

COVID-19 admissions were more likely to be referred to the critical care outreach team (14.7% vs 3.6%, p<0.001), admitted to the intensive care unit (ICU) (6.8% vs 2.5%) and referred to palliative care (10.5% vs 4.9%). They also had longer hospital stay (7.3 days vs 3.0 days, p<0.001) and higher in-hospital mortality (32.1% vs 5.8%, p<0.001).

Figure 1 shows the relationship between continuous covariates and the observed risk of in-hospital mortality in COVID-19 versus non-COVID-19 admissions. Whilst the pattern of mortality was broadly similar between COVID-19 and non-COVID-19 admissions, COVID-19 admissions had a consistently higher risk of mortality for the range of covariate values (see Figure 1 and Figure S2 in supplementary material). Figure 1 also shows that although increasing NEWS and NEWS2 scores reflected increased mortality, but for any given value of NEWS or NEWS2 the risk of mortality for COVID-19 was on average 24% higher and at a NEWS or NEWS2 of 5 the risk of mortality in COVID-19 vs non-COVID-19 was 36% versus 9%.

The performance of index NEWS2 to predict the risk of death (24hour, 48hour, 72hour, in-hospital) in COVID-19 and non-COVID-19 admissions is shown in Figure 2 and Table S4. The c-statistics for predicting in-hospital mortality in COVID-19 admissions was significant lower than for patients without COVID-19 (NEWS: 0.64 vs 0.74; NEWS2: 0.64 vs 0.74), however these differences reduced at 72hours (NEWS: 0.75 vs 0.81; NEWS2: 0.71 vs 0.81), 48 hours (NEWS: 0.78 vs 0.81; NEWS2: 0.76 vs 0.82) and 24hours (NEWS: 0.84 vs 0.84; NEWS2: 0.86 vs 0.84). We found the same performance for medical and

surgical admissions (see Table S5 in supplementary material). Figure S3 (in supplementary material) shows Kaplan-Meier curve for mortality for COVID-19 and non-COVID-19 admissions.

Table 2 includes the sensitivity, specificity, positive and negative predictive values for NEWS and NEWS2 for COVID-19 and non-COVID-19 patients. NEWS2 had higher sensitivity but lower specificity compared to NEWS.

Characteristic	COVID-19	Non-COVID-19	p-value
N	620	5824	-
Male (%)	339 (54.7)	2918 (50.1)	0.033
Mean Age [years] (SD)	73.3 (15.4)	67.7 (19)	<0.001
Admission type			<0.001
Medical	588 (94.8)	4727 (81.1)	
Surgical	32 (5.2)	1097 (18.9)	
Ethnicity			<0.001
White	465 (75)	4668 (80.2)	
Black, Asian, and other minority ethnic	34 (5.5)	152 (2.6)	
Missing	121 (19.5)	1004 (17.2)	
Median BMI (IQR)* [kg/m^2]	27.5 (8.4)	26 (7.6)	<0.001
Mean NEWS (SD)	4 (2.8)	2.5 (2.3)	<0.001
Mean NEWS2 (SD)	4.6 (3)	2.8 (2.7)	<0.001
Vital Signs			
Mean Respiratory rate [breaths per minute] (SD)	23.5 (6.6)	19.8 (5)	<0.001
Mean Temperature [oC] (SD)	36.8 (1.1)	36.3 (0.9)	<0.001
Mean Systolic pressure [mmHg] (SD)	136.1 (25.8)	142.5 (29.2)	<0.001
Mean Diastolic pressure [mmHg] (SD)	76.5 (16.3)	79.4 (16.8)	<0.001
Mean Pulse rate [beats per minute] (SD)	92.2 (22.1)	88.5 (22.2)	<0.001
Mean % Oxygen saturation (SD)	94.8 (4.4)	96.4 (2.9)	<0.001
Oxygen supplementation (%)	207 (33.4)	667 (11.5)	<0.001
Mean Oxygen flow rate [Litre per minute] (SD)	7.6 (5.8)	6.4 (5.5)	0.008
Oxygen scale 2 (%)	42 (6.8)	361 (6.2)	0.634
Alertness			<0.001
Alert (%)	514 (82.9)	5239 (90)	
Baseline confusion (%)	5 (0.8)	45 (0.8)	
New confusion (%)	19 (3.1)	82 (1.4)	
Pain (%)	0 (0)	49 (0.8)	
Voice (%)	58 (9.4)	227 (3.9)	
Unconscious (%)	24 (3.9)	182 (3.1)	
Referred to critical care outreach team (%)	91 (14.7)	211 (3.6)	<0.001
Admission to ICU (%)	42 (6.8)	147 (2.5)	<0.001
Palliative care (%)	65 (10.5)	288 (4.9)	<0.001
On ventilation (%)	18 (2.9)	12 (0.2)	<0.001
Median Length of Stay (days) (IQR)	7.3 (11.7)	3 (5.5)	<0.001
Mortality within 24 hours (%)	9 (1.5)	53 (0.9)	0.273
Mortality within 48 hours (%)	15 (2.4)	94 (1.6)	0.189

Mortality within 72 hours (%)	33 (5.3)	131 (2.3)	<0.001
In-hospital Mortality	199 (32.1)	336 (5.8)	<0.001

Table 1 Characteristics of emergency medical admissions in COVID-19 versus non-COVID-19

** BMI is missing 188 (30.3%) for COVID and 2283 (39.2%) for non-COVID*

Mortality type	Models	COVID-19							Non-COVID-19						
		N*	Sensitivity%	Specificity%	PPV	NPV	LR+	LR-	N*	Sensitivity%	Specificity%	PPV	NPV	LR+	LR-
In-hospital	NEWS	183	45.7 (38.7 to 52.9)	78.1 (73.9 to 82)	49.7 (42.3 to 57.2)	75.3 (71 to 79.3)	2.1 (1.7 to 2.6)	0.7 (0.6 to 0.8)	710	40.8 (35.5 to 46.2)	89.6 (88.7 to 90.4)	19.3 (16.5 to 22.4)	96.1 (95.5 to 96.6)	3.9 (3.4 to 4.5)	0.7 (0.6 to 0.7)
In-hospital	NEWS2	300	62.8 (55.7 to 69.5)	58.4 (53.6 to 63.2)	41.7 (36 to 47.5)	76.9 (71.9 to 81.4)	1.5 (1.3 to 1.8)	0.6 (0.5 to 0.8)	1300	59.2 (53.8 to 64.5)	79.9 (78.9 to 81)	15.3 (13.4 to 17.4)	97 (96.4 to 97.5)	3 (2.7 to 3.3)	0.5 (0.4 to 0.6)
Within 24 hours	NEWS	183	88.9 (51.8 to 99.7)	71.4 (67.6 to 74.9)	4.4 (1.9 to 8.4)	99.8 (98.7 to 100)	3.1 (2.4 to 4)	0.2 (0 to 1)	710	60.4 (46 to 73.5)	88.3 (87.4 to 89.1)	4.5 (3.1 to 6.3)	99.6 (99.4 to 99.7)	5.1 (4.1 to 6.5)	0.4 (0.3 to 0.6)
Within 24 hours	NEWS2	300	88.9 (51.8 to 99.7)	52.2 (48.2 to 56.2)	2.7 (1.2 to 5.2)	99.7 (98.3 to 100)	1.9 (1.5 to 2.4)	0.2 (0 to 1.4)	1300	77.4 (63.8 to 87.7)	78.2 (77.1 to 79.2)	3.2 (2.3 to 4.3)	99.7 (99.5 to 99.9)	3.5 (3 to 4.1)	0.3 (0.2 to 0.5)
Within 48 hours	NEWS	183	80 (51.9 to 95.7)	71.7 (68 to 75.3)	6.6 (3.4 to 11.2)	99.3 (98 to 99.9)	2.8 (2.1 to 3.8)	0.3 (0.1 to 0.8)	710	54.3 (43.7 to 64.6)	88.5 (87.6 to 89.3)	7.2 (5.4 to 9.3)	99.2 (98.9 to 99.4)	4.7 (3.9 to 5.8)	0.5 (0.4 to 0.6)
Within 48 hours	NEWS2	300	86.7 (59.5 to 98.3)	52.6 (48.5 to 56.6)	4.3 (2.3 to 7.3)	99.4 (97.8 to 99.9)	1.8 (1.5 to 2.3)	0.3 (0.1 to 0.9)	1300	73.4 (63.3 to 82)	78.5 (77.4 to 79.6)	5.3 (4.2 to 6.7)	99.4 (99.2 to 99.6)	3.4 (3 to 3.9)	0.3 (0.2 to 0.5)
Within 72 hours	NEWS	183	69.7 (51.3 to 84.4)	72.7 (68.9 to 76.3)	12.6 (8.1 to 18.3)	97.7 (95.8 to 98.9)	2.6 (2 to 3.3)	0.4 (0.2 to 0.7)	710	52.7 (43.8 to 61.5)	88.7 (87.9 to 89.6)	9.7 (7.6 to 12.1)	98.8 (98.4 to 99.1)	4.7 (3.9 to 5.6)	0.5 (0.4 to 0.6)
Within 72 hours	NEWS2	300	78.8 (61.1 to 91)	53.3 (49.2 to 57.4)	8.7 (5.7 to 12.4)	97.8 (95.5 to 99.1)	1.7 (1.4 to 2.1)	0.4 (0.2 to 0.8)	1300	73.3 (64.8 to 80.6)	78.9 (77.8 to 79.9)	7.4 (6 to 8.9)	99.2 (98.9 to 99.5)	3.5 (3.1 to 3.9)	0.3 (0.3 to 0.5)

Table 2 Sensitivity analysis of NEWS versus NEWS2 in predicting the risk in-hospital mortality, mortality within 24 hours, 48 hours, and 72 hours at NEWS (or NEWS2)≥5 in the COVID-19 and Non-COVID-19 medical admissions. PPV=Positive Predictive Value; NPV= Negative Predictive Value; LR+=Positive Likelihood Ratio; LR-=Negative Likelihood Ratio; N* = Number of positive cases identified by model at NEWS (or NEWS2)≥5.

Discussion

Whilst NEWS and NEWS2 are recommended for monitoring patients with COVID-19, we found that the index or on-admission NEWS/NEWS2 offered lower discrimination for COVID-19 patients versus non-COVID-19 patients. We also found that the index NEWS2 was not better than index NEWS. For each value of the index NEWS/NEWS2, COVID-19 patients had a substantially higher risk of in-hospital mortality than non-COVID-19 patients, which equated to an average 24% risk difference which reflects the higher baseline risk of mortality in our COVID-19 patients. However, the c-statistics for the index NEWS/NEWS2 improved with shorter time horizons with the highest discrimination (above 0.8) being seen for predicting mortality risk within 24hours of the index NEWS/NEWS2.

A recent paper by Kostakis et al [7], found good discrimination for NEWS or NEWS2 (c-statistics 0.842-0.894) concluding that their results "support the national and international recommendations for the use of NEWS or NEWS2 for the assessment of acute-illness severity in patients with COVID-19." In contrast to our approach, Kostakis et al [7] used the last or ultimate recorded NEWS2/NEWS within 24 hours of death or ICU admission. We note that when we consider death within 24 hours of admission, our reported c-statistics for index NEWS/NEWS2 are comparable with those of Kostakis et al [7].

So taken together these findings indicate that care must be taken not to interpret the predictive power of the ultimate NEWS or NEWS2 score (taken within 24 hours of death) as being equivalent to the predictive power of the index NEWS or NEWS2 score (or preceding NEWS or NEWS2 scores) for risk of in-hospital mortality. The ultimate NEWS or NEWS2 is an accurate predictor of mortality (plus ICU admission in the case of Kostakis et al) for COVID-19 patients but offers a maximum of 24hours for appropriate interventions. This good performance is less surprising when we note that, with the exception of patients who are characterised by abnormal physiology (patients recovering from end-stage renal failure or patients recovering from brain injury), "Patients die not from their disease but from the disordered physiology caused by the disease." [17]. But, as our findings show, the performance of the index NEWS or index NEWS2 for predicting death in hospital, which offers an early window of opportunity for assessment and intervention, is poorer especially for COVID-19 patients. This needs to be brought to the attention of medical and nursing staff and reflected in escalation protocols and guidelines (which have always highlighted the importance of clinical judgement) to mitigate potential threats to patient safety by promoting situational awareness about the actual, on admission, in-hospital mortality risk for COVID-19 patients.

The World Health Organisation (WHO) describes the range of symptoms seen in COVID-19 which include (but are not limited to) dyspnoea, reduced alertness, delirium, fever, tachypnoea and hypoxia

(as a common sign in moderate to severe disease). These symptoms are included in the physiological observation set underpinning NEWS and NEWS2 and were more frequent in our COVID-19 patients compared to non-COVID-19 patients. We also found evidence of lower blood pressure and a higher pulse rate in COVID-19 patients. The NEWS2 guidelines[8] do note that patients with COVID-19 can develop 'silent hypoxia' where oxygen saturations can drop to low levels and precipitate acute respiratory failure quickly without the presence of obvious symptoms of respiratory distress. As such any patients admitted and on supplemental oxygen may develop a rapidly increasing oxygen requirement that may not increase the NEWS2 score. It is stressed that any increase in oxygen requirement should trigger an escalation for review by a competent senior decision-maker [8].

Consideration should be also be given to enhancing NEWS or NEWS2 so that they can be used in COVID-19 and non-COVID-19 patients rather than needing to change scoring systems or adjust estimations of risk dependent on diagnosis. We have previously demonstrated how a fully automated computer-enhanced NEWS score can be developed which requires no additional data collection and builds on the standardisation provided by NEWS [18]. We now propose to extend this to include COVID-19 status.

There are several limitations to our study. (1) This study data is from a single NHS Trust and the extent to which these findings are generalisable, especially to minority ethnic groups with higher COVID-19 mortality, needs further study. (2) We used the index NEWS2 which reflects the 'on-admission' risk of mortality of the patients. Nonetheless, NEWS2 is repeatedly updated for each patient according to local hospital protocols, and the extent to which changes in NEWS2 over time reflect changes in mortality risk needs further study. (3) Although we found no evidence of NEWS2 as having a superior performance to NEWS, it is important to note that our index NEWS data are hypothetical in the sense that the Trust has been using NEWS2 since April 2019. Nevertheless, it is worth noting that a recent, albeit small Italian study based on 71 hospitalised COVID-19 patients found NEWS2 to be a good predictor (with a high c-statistic 0.90) of subsequent ICU admission for COVID-19 patients but was not able to consider mortality because of insufficient events [6]. Our study did not consider ICU admissions as an outcome because the number of ICU admissions were low but Kostakis et al [7] used it as a composite outcome with in-hospital mortality (5).

Conclusions

The index or on-admission NEWS and NEWS2 offer lower discrimination for COVID-19 admissions versus non-COVID-19 admissions. The index NEWS2 is not better than the index NEWS. For each value

of the index NEWS/NEWS2, COVID-19 admissions had a substantially higher risk of mortality than non-COVID-19 admissions which reflects the increased baseline mortality risk of COVID-19.

Contributorship

DR & MAM had the original idea for this work. MF undertook the statistical analyses with guidance from MAM. MFi & KB extracted the necessary data frames. DR gave a clinical perspective. DR, MF and MAM wrote the first draft of this paper and all authors subsequently assisted in redrafting and have approved the final version.

Competing Interests

The authors declare no conflicts of interest.

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Data Availability Statement

Our data sharing agreement with NHS York hospital trust does not permit us to share this data with other parties. Nonetheless if anyone is interested in the data, then they should contact the R&D offices in the first instance.

Figure 1 Line plots showing the observed risk of in-hospital mortality with continuous covariates for COVID-19 (black colour) and Non-COVID-19 (grey colour) admissions.

Note: Size of circles reflects sample size independently in the COVID-19 and non-COVID-19 groups.

Figure 2 Receiver Operating Characteristic curve for NEWS2 and NEWS in predicting the risk of in-hospital mortality, mortality within 24 hours, 48 hours, and 72 hours in the COVID-19 (black colour) and Non-COVID-19 (grey colour) admissions.

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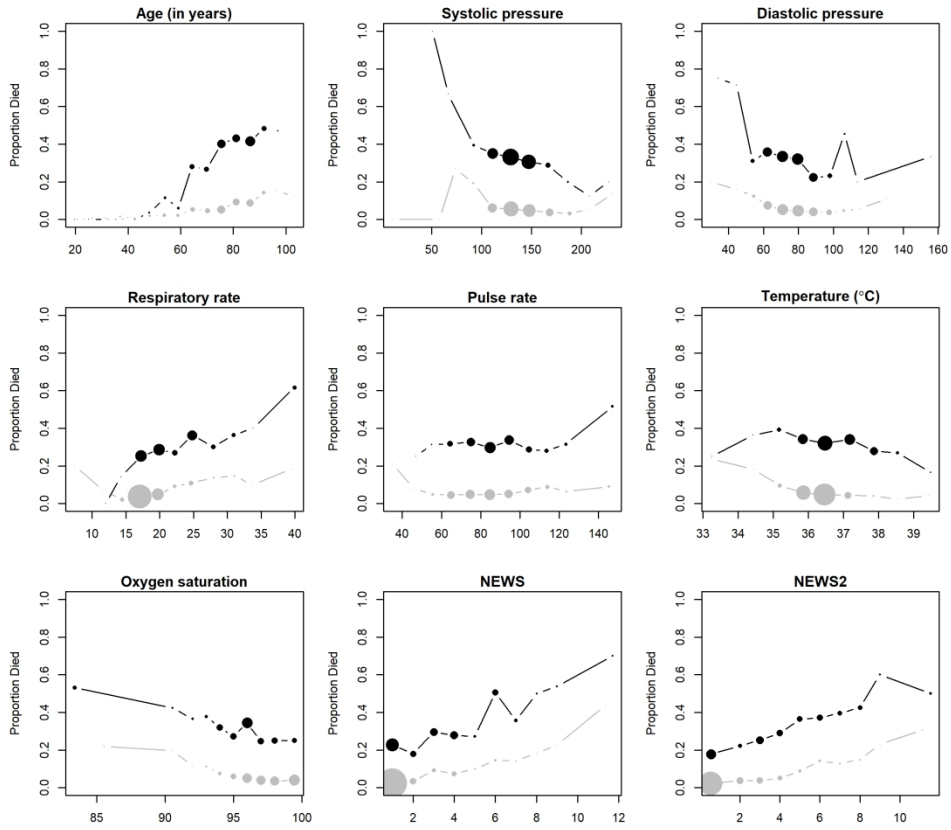
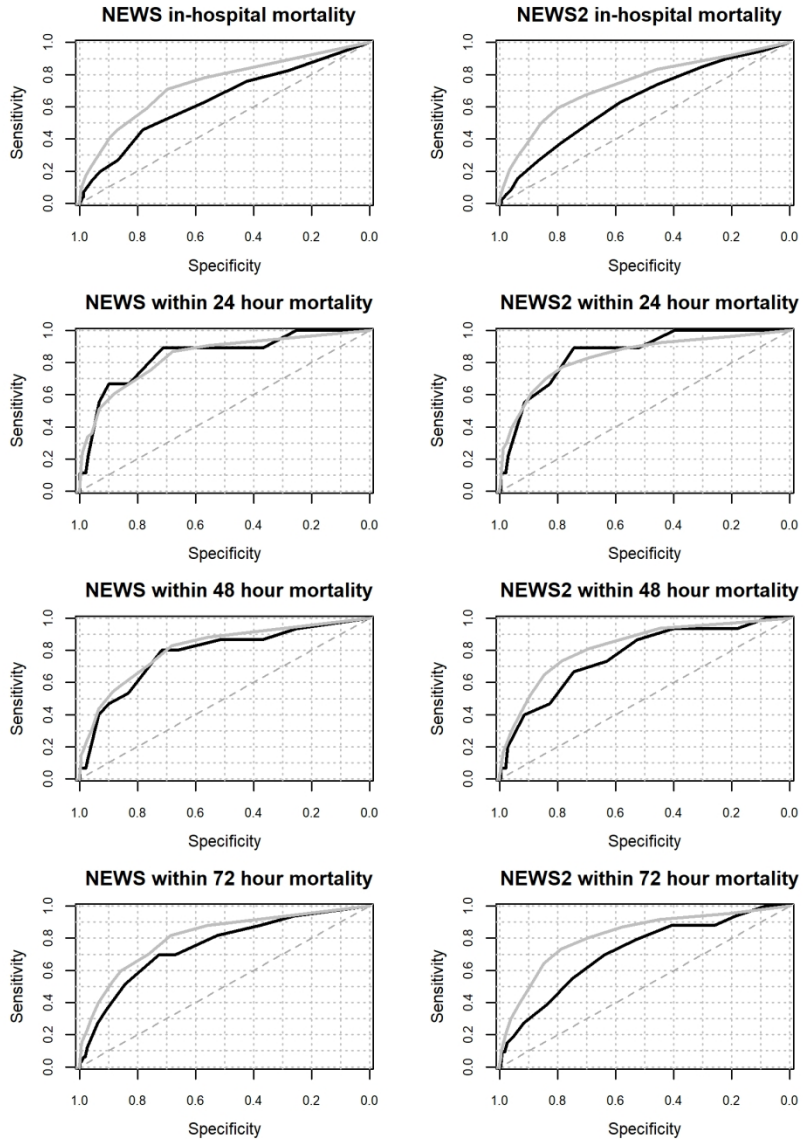


Line plots showing the observed risk of in-hospital mortality with continuous covariates for COVID-19 (black colour) and Non-COVID-19 (grey colour) admissions.
Note: Size of circles reflects sample size independently in the COVID-19 and non-COVID-19 groups.

228x203mm (300 x 300 DPI)



Receiver Operating Characteristic curve for NEWS2 and NEWS in predicting the risk of in-hospital mortality, mortality within 24 hours, 48 hours, and 72 hours in the COVID-19 (black colour) and Non-COVID-19 (grey colour) admissions.

152x203mm (300 x 300 DPI)

Table S1: NEWS scoring chart

Physiological Parameters	3	2	1	0	1	2	3
Respiration rate	≤8		9 - 11	12 - 20		21 - 24	≥25
Oxygen saturations	≤91	92 - 93	94 - 95	≥96			
Any supplemental Oxygen		Yes		No			
Temperature	≤35.0		35.1 - 36.0	36.1 - 38.0	38.1 - 39.0	≥39.1	
Systolic BP	≤90	91 - 100	101 - 110	111 - 219			≥220
Heart rate	≤40		41 - 50	51-90	91 - 110	111 - 130	≥131
Level of consciousness				Alert			Voice, Pain, or Unconscious

Table S2: NEWS2 scoring chart

Physiological Parameters	3	2	1	0	1	2	3
Respiration rate	≤8		9 - 11	12 - 20		21 - 24	≥25
SpO2 Scale 1 (%)	≤91	92 - 93	94 - 95	≥96			
SpO2 Scale 2 (%)	≤83	84 - 85	86 - 87	88 - 92 ≥93 on Air	93 – 94 on oxygen	95 – 96 on oxygen	≥97 on oxygen
Oxygen saturations	≤91	92 - 93	94 - 95	≥96			
Air or Oxygen?		Oxygen		Air			
Temperature	≤35.0		35.1 - 36.0	36.1 - 38.0	38.1 - 39.0	≥39.1	
Systolic BP	≤90	91 - 100	101 - 110	111 - 219			≥220
Heart rate	≤40		41 - 50	51-90	91 - 110	111 - 130	≥131
Level of consciousness				Alert			Voice, Pain, Confusion, or Unconscious

The NEWS [https://www.rcplondon.ac.uk/projects/outputs/national-early-warning-score-news] is based on a scoring system in which a score is allocated to the physiological measurements of vital signs already undertaken when patients present to or are being monitored in hospital. A score is allocated to each as they are measured with the magnitude of the score reflecting how extreme the parameter varies from the norm. This score is then aggregated and uplifted for people requiring oxygen.

Characteristic	COVID-19	Non-COVID-19	All
	N (%)	N (%)	N (%)
Total emergency medical discharges between 11 Mar 20 to 13 June 20	622 (9.6%)	5858 (90.4%)	6480 (100%)
Excluded: No NEWS recorded (%)	0 (0.0)	19 (0.3)	19 (0.3)
Excluded: First NEWS after 24 hours of admission (%)	2 (0.3)	15 (0.3)	17 (0.3)
Total excluded (%)	2 (0.3)	34 (0.6)	36 (0.6)
Total included (%)	620 (99.7)	5824 (99.4)	6444 (99.4)

Table S3 Number of emergency medical admissions included/excluded

Mortality timepoint		COVID-19				Non-COVID-19			
	Model	Risk discharged alive	Risk discharged deceased	Risk Differ-ence	AUC (95% CI)	Risk discharged alive	Risk discharge-ed deceased	Risk Differ-ence	AUC (95% CI)
In-hospital Mortality	NEWS	0.11	0.16	0.06	0.64 (0.59 to 0.69)	0.07	0.17	0.09	0.74 (0.71 to 0.77)
	NEWS2	0.11	0.15	0.04	0.64 (0.59 to 0.68)	0.07	0.16	0.09	0.74 (0.71 to 0.77)
Mortality within 24 hours	NEWS	0.12	0.32	0.20	0.84 (0.7 to 0.99)	0.08	0.25	0.17	0.84 (0.78 to 0.89)
	NEWS2	0.12	0.28	0.16	0.86 (0.75 to 0.97)	0.08	0.24	0.16	0.84 (0.78 to 0.9)
Mortality within 48 hours	NEWS	0.12	0.26	0.14	0.78 (0.65 to 0.91)	0.08	0.22	0.14	0.81 (0.77 to 0.86)
	NEWS2	0.12	0.23	0.11	0.76 (0.64 to 0.89)	0.08	0.21	0.14	0.82 (0.78 to 0.87)
Mortality within 72 hours	NEWS	0.12	0.23	0.11	0.75 (0.66 to 0.84)	0.08	0.21	0.13	0.81 (0.77 to 0.85)
	NEWS2	0.12	0.21	0.09	0.71 (0.62 to 0.8)	0.08	0.21	0.13	0.82 (0.78 to 0.85)

Table S4 Area under the Receiver Operating Characteristic curve in predicting mortality (in-hospital, 24hour, 48hour, 72hour) at index NEWS2 (or NEWS) ≥ 5 in COVID-19 and non-COVID-19 emergency medical admissions

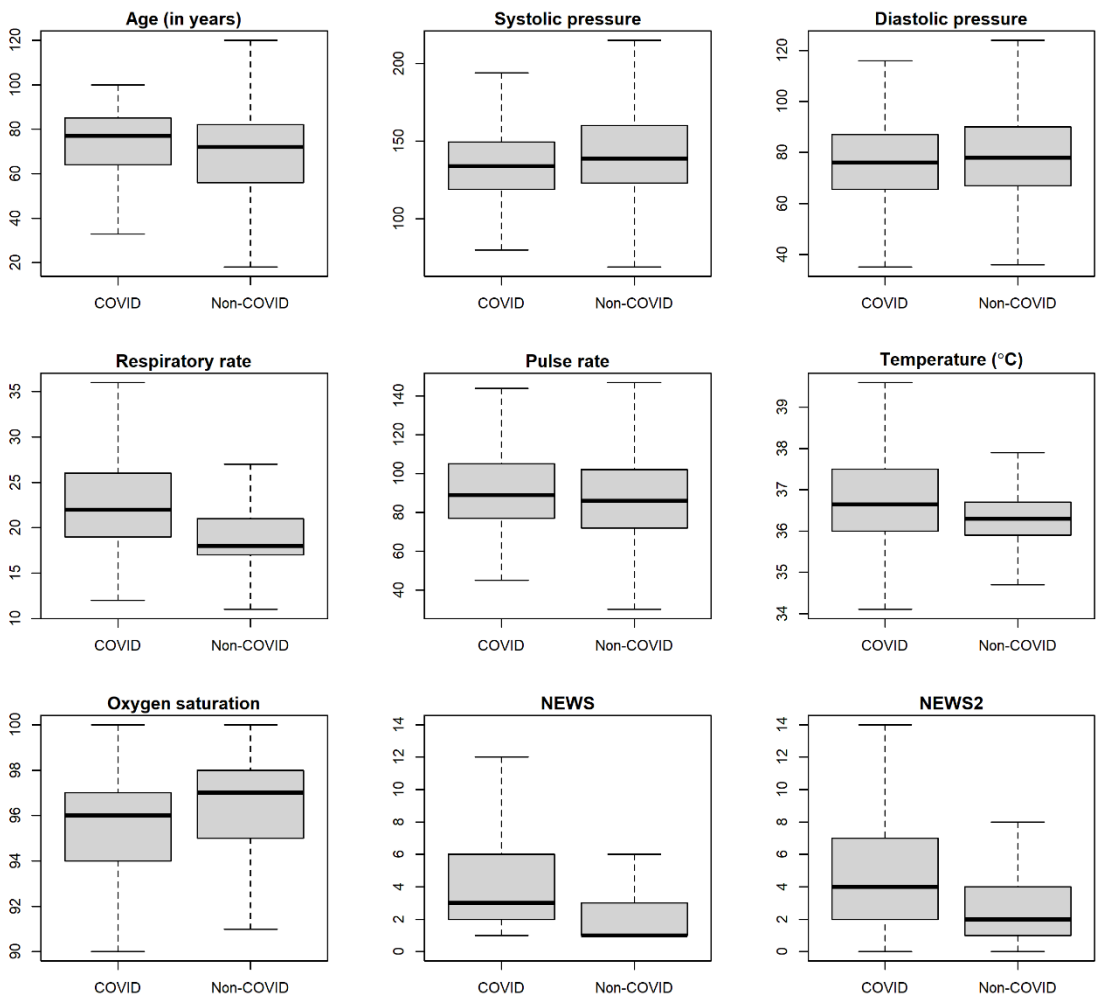


Figure S1 Boxplots without outliers for continuous covariates for COVID-19 versus non-COVID-19 admissions

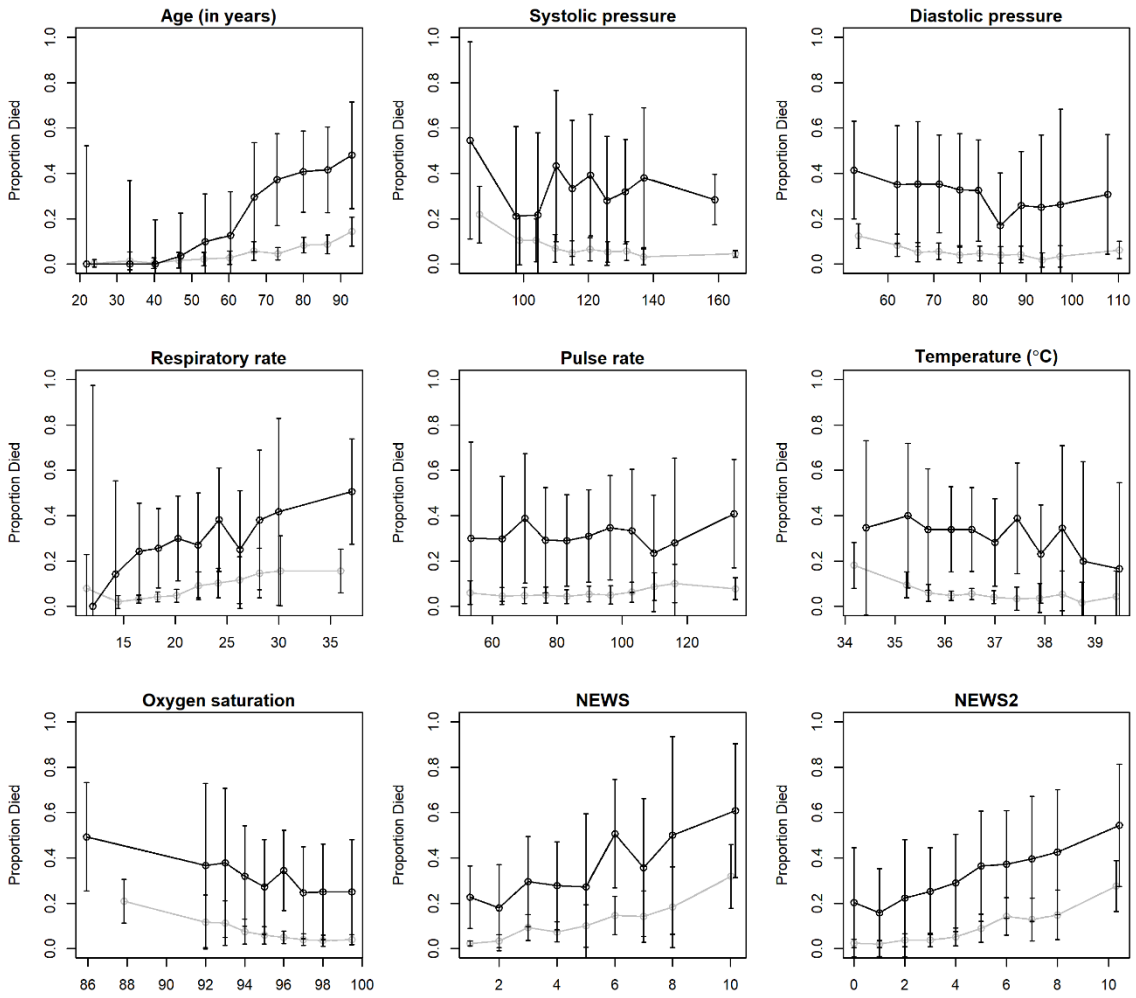


Figure S2 Line plots showing the observed risk of in-hospital mortality (95% confidence intervals) with continuous covariates for COVID-19 versus non-COVID-19 admissions

Admission type	Medical N= 5313		Surgical N=1129		Both N=6444	
	COVID+	COVID-	COVID+	COVID-	COVID+	COVID-
Number of admission (N)	588	4727	32	1097	620	5824
AUC (95% CI) for NEWS	0.64 (0.60 -0.69)	0.74 (0.71 -0.77)	0.63 (0.43 -0.83)	0.71 (0.63 -0.80)	0.64 (0.60 -0.69)	0.74 (0.71 -0.77)
AUC (95% CI) for NEWS 2	0.64 (0.60 -0.69)	0.73 (0.70 -0.77)	0.65 (0.46 -0.85)	0.74 (0.65 -0.82)	0.64 (0.60 -0.69)	0.74 (0.71 -0.77)

Table S5: Performance of NEWS and NEWS in predicting the in-hospital mortality in medical and surgical admission.

COVID+ = COVID-19 admissions; COVID- = Non-COVID-19 admissions

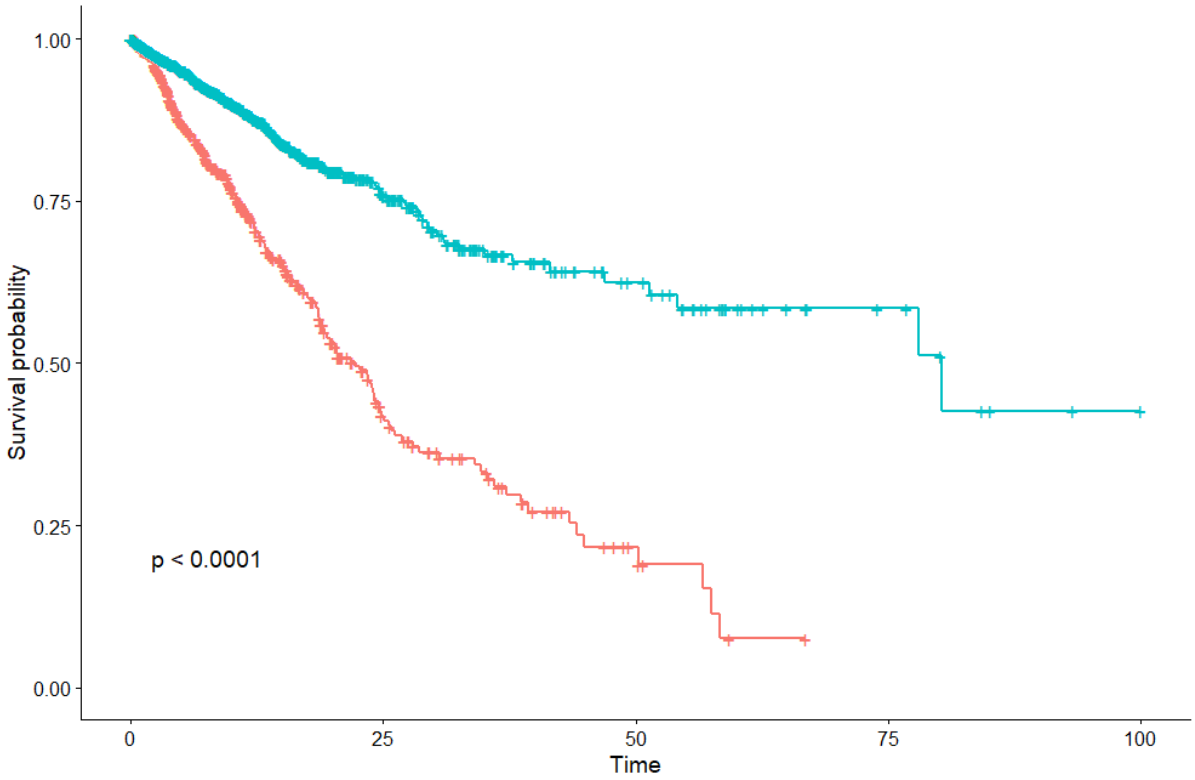


Figure S3 Kaplan-Meier curve for predicting mortality with 95% confidence intervals for COVID-19 versus non-COVID-19 admissions

COVID-19 admissions shown in green colour and non-COVID-19 admissions shown in red colour.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **p1,2**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **p2**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **p4**
Objectives	3	State specific objectives, including any prespecified hypotheses **p4**
Methods		
Study design	4	Present key elements of study design early in the paper **p5**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **p5**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants **p5**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **p5**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **p5**
Bias	9	Describe any efforts to address potential sources of bias **p5**
Study size	10	Explain how the study size was arrived at **p5**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **p5**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **p6**
		(*b*) Describe any methods used to examine subgroups and interactions **p6**
		(*c*) Explain how missing data were addressed **p6**
		(*d*) If applicable, describe analytical methods taking account of sampling strategy **p6**
		(*e*) Describe any sensitivity analyses **p6**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **p7**, **appendix Table S3**
		(b) Give reasons for non-participation at each stage **p7**, **appendix Table S3**
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **p7,8**
		(b) Indicate number of participants with missing data for each variable of interest **p6**, **appendix Table S3**
Outcome data	15*	Report numbers of outcome events or summary measures **p7,8**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **p7,8**
		(*b*) Report category boundaries when continuous variables were categorized

		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **p7,8**
Discussion		
Key results	18	Summarise key results with reference to study objectives **p11**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **p11**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **p11**
Generalisability	21	Discuss the generalisability (external validity) of the study results **p11,12**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **p13**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.