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Validity of the UK Early Access to Medicines Scheme Criteria for Remdesivir use in patients with COVID-19 disease

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Dear Editor,

The UK Medicines and Healthcare Products Regulatory Agency (MHRA) released its Early Access to Medicines Scheme (EAMS) criteria for the use of Remdesivir in patients with COVID-19 on May 26th, 2020.[1] The MHRA Scientific Opinion supports the use of Remdesivir in patients with severe disease. However, given current limitations in drug supply, an interim risk score has been proposed to identify those patients thought most likely to benefit from the drug.

The score includes eight variables: radiographic severity score > 3, male gender, non-white ethnicity, diabetes, hypertension, neutrophils >8.0 10/L, age >40 and CRP >40.[1] It seems to have first been developed for a recently launched COVID-19 immune modulator therapy trial (TACTIC-R),[2] based on an initial unpublished cohort of 200 patients.[3] An adapted version of the risk score, with twelve variables, was used to predict clinical deterioration (i.e. death or admission to critical care) in a cohort of 1,157 confirmed COVID-19 patients in one London NHS Trust.[4] This score showed good performance, with an area under the receiver operating curve (AUROC) of 71.2% (test data).[4] The findings were published in this journal, which we read with interest.

However, how the score proposed by EAMS performs in front-line settings and its implications for how many patients will likely receive Remdesivir for COVID-19 is currently unknown.

We evaluated the performance of the EAMS criteria in a cohort of 517 patients COVID-19 confirmed patients admitted to Imperial College Healthcare Trust between the start of the pandemic and 5th

April 2020.[5] We found that 348 patients in our cohort would have met criteria to be considered for Remdesivir therapy (i.e. age > 12, weight >=40kg, creatinine clearance >50ml/min and AST/ALT <5 x ULN or no history of Childs Pugh C liver cirrhosis).

According to the EAMS score, 262 (75.3%) of the eligible patients in our cohort would have been classified as high-risk and 86 (24.7%%) as low-risk. The composite risk of death or ITU admission was 2.58 times greater (95%CI 1.56-4.25, p < 0.001) for the high- compared to the low-risk group (Figure 1a). The performance of the score was reasonable when considering the AUROC of 71.1% (p<0.001) (Figure 1b). However, the overall misclassification of outcome was of 45.7%, with 14 (4.0%) patients who deteriorated classified as low-risk and 145 (41.7%) who did not deteriorate as high-risk, which has potential implications for allocation of a scarce resource. Common characteristics of those classified as low-risk that subsequently deteriorated included being female, white and having a non-severe appearance by chest X-ray (Table 1). Additionally, of the eight individual covariates in the full predictive model proposed by EAMS, only RALE score and CRP levels were statistically significant in predicting the composite outcome in our cohort (Table 2).

Also of note, 169 patients in our cohort did not meet initial EAMS eligibility criteria for Remdesivir. The majority (n=160) would have been excluded due to a creatinine clearance <50mL/min, 1 based on age, 1 for weight and 7 for known cirrhotic liver disease. The crude incidence rate of deterioration in this group was of 47.9% and, if the EAMS score would have been applied, it would not have differentiated the risk of deterioration between those classified as high or low-risk (RR 1.43, 95%CI 0.87-2.36, p=0.12). Worryingly, their crude incidence rate of deterioration was similar to the high-risk group meeting inclusion criteria, at 42.0%. This highlights an important group of patients with renal impairment with poor COVID-19 outcomes who are often excluded from clinical trials.

We acknowledge the urgent need to be responsive to the rapidly changing context, given the enormous public health implications of treatment allocation decisions based on clinical criteria. Nevertheless, the release of the EAMS criteria based on a single cohort of patients seems premature. While reassuring that the scoring system seems show reasonable performance in identifying most of those at high risk of adverse outcomes in our cohort, 11.3% of those who deteriorate and met inclusion criteria were missed by this score. Moreover, amongst those not meeting inclusion criteria, the score was not able to accurately predict outcome, highlighting the urgent need to identify safe treatments for use in those with renal and/or hepatic impairment. Importantly, in both the adapted risk criteria published previously in this journal and in those proposed by our group, hypalbuminaemia, reduced glomerular filtration and admission hypoxia (among other parameters) were also important predictors of worse hospitalisation outcomes.[4,5] None of these parameters are included in the EAMS criteria, which could improve the misclassification issues observed. However, rationalising the number of parameters included for a scoring system intended for front-line clinical use should be carefully assessed to maximise its utility and limit increasing workload for already overstretched clinical teams.

It has to be hoped that access to Remdesivir for all who may benefit from it will be achievable in coming months as manufacturing capacity expands. In the meantime, criteria for eligibility should be refined based on data from a wide range of clinical settings and shared as quickly as possible to ensure a finite resource is used as rationally as possible.

Conflicts of interest: None to declare.

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Keywords: COVID-19, mortality, clinical deterioration, risk score, remdesivir

References

1 UK Department of Health & Social Care. Early Access to Medicines Scheme for remdesivir in the treatment of COVID-19. 2020; published online May 26. https://www.gov.uk/government/publications/early-access-to-medicines-scheme-eams-scientific-opinion-remdesivir-in-the-treatment-of-patients-hospitalised-with-suspected-or-laboratory-confirmed (accessed May 25, 2020).

2 Hall F, Jayne D. Multi-Arm Therapeutic Study in Pre-ICU Patients Admitted with COVID-19. 2020. https://cctu.org.uk/portfolio/COVID-19/TACTIC/TACTIC-R (accessed May 26, 2020).

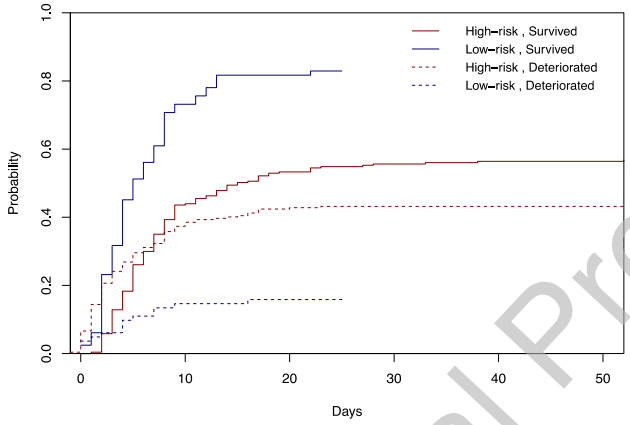
3 Sneep R, Cantle F, Brookes A *et al.* Early Epidemiological and Clinical Analysis of the First 200 Patients with COVID-19 Admitted via the Emergency Department in King's College Hospital, London: A Retrospective Cohort Stodu (4/9/20). Available at Available at SSRN: https://ssrn.com/abstract=3576791 or http://dx.doi.org/10.2139/ssrn.3576791

4 Galloway JB, Norton S, Barker RD, *et al.* A clinical risk score to identify patients with COVID-19 at high risk of critical care admission or death: an observational cohort study. *Journal of Infection* 2020; : S0163445320303145.

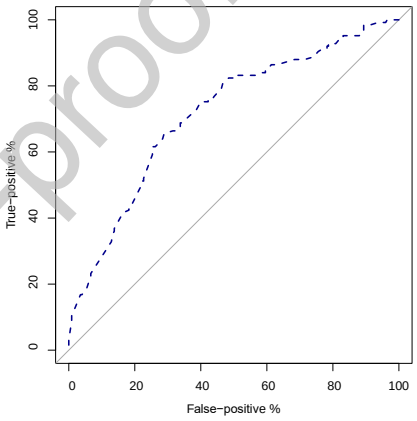
5 Perez Guzman P, Daunt A, Mukherjee S, *et al.* Report 17: Clinical characteristics and predictors of outcomes of hospitalised patients with COVID-19 in a London NHS Trust: a retrospective cohort study. Imperial College London, 2020 DOI:10.25561/78613.

Figure 1: EAMS criteria's performance amongst the ICHNT cohort of COVID-19 patients.

a) Cumulative incidence of discharge alive vs death by risk classification; b) receiver operating characteristic curve.



a.



b.

Table 1: Characteristics of patients who deteriorated by classification outcome by EAMS criteria.

*High- and low-risk as per EAMS criteria; deterioration defined as admission to ITU or death.

	Patients scored as '*low-risk*' who deteriorated* N = 14 (4.02\%)	Patients scored as *'high-risk'* who did not deteriorate* N = 110 (31.61\%)
Age > 40	12 (85.71\%)	103 (93.64\%)
Male sex	4 (28.57\%)	83 (75.45\%)
Non-White ethnicity	4 (28.57\%)	81 (73.64\%)
Diabetes	1 (7.14\%)	23 (20.91\%)
Hypertension	0 (0.00\%)	44 (40.00\%)
Neutrophils > 8 x 10/L	4 (28.57\%)	28 (25.45\%)
CRP > 40 mg/L	10 (71.43\%)	103 (93.64\%)
RALE score > 3	1 (7.14\%)	94 (85.45\%)