ORIGINAL ARTICLE

PREDICTING DEVELOPMENT OF CRITICAL ILLNESS IN PATIENTS WITH COVID-19 PRESENTING TO A TERTIARY CARE HOSPITAL IN A DEVELOPING COUNTRY

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Background: With the increasing number of COVID-19 patients and limited resources available to accommodate them, there is a need for risk stratification tools to ensure better utilization of resources. **Methods:** We conducted a retrospective observational cohort study in patients discharged from the COVID designated areas of a large tertiary care hospital in Karachi, Pakistan from the 1st of May to the 31st of July, 2020. 581 patients were included and the COVID GRAM score was calculated at the time of admission and patients developing critical disease as per COVID GRAM study criteria (need of intensive care unit admission, invasive ventilation or death) after 24 hours of admission were noted. **Results:** The mean age of the study population was 56.3±14.8 years. Patients that developed critical illness (as per COVID GRAM study criteria) beyond 24 hours after admission had higher COVID GRAM scores at admission versus those that did not (183.2±80.7 versus 130.3±42.6). The Area under the Receiver Operator Curve for the COVID gram score to predict critical illness in the study population was 0.802 (95% confidence interval, 0.753–0.850). On binary logistic multivariable regression analysis, the COVID GRAM and SOFA scores on admission and need of ICU admission during hospitalization were significant predictors of mortality 24 hours after admission. **Conclusion:** The COVID GRAM score is a useful risk assessment tool and can be used for appropriate allocation and prioritization of resources where they are most needed.

Keywords: COVID-19; Prognostic factors; Critical illness; Mortality; Outcome's assessment

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INTRODUCTION

Severe Acute Respiratory Syndrome (SARS) CoV2 emerged as pneumonia of unknown cause from the Hubei Province, China in late 2019. It was declared a Public Health Emergency of International Concern on the 30th of January, 2020 and a Pandemic on the 11th of March, 2020 by the World Health Organization (WHO).[1]

As it quickly spread affecting millions of people worldwide, the spectrum of disease it caused was noted to be variable. In some patients it remained asymptomatic while others developed a life-threatening illness. A study from China showed that patients with severe and critical COVID-19 were in the higher age bracket, males, and with comorbid disease, most commonly hypertension.[2] Laboratory parameters showed higher levels of C- Reactive Protein (CRP), Lactate Dehydrogenase (LDH), Aspartate Aminotransferase (AST), Alanine Transaminase (ALT) and D-dimer levels in patients with severe disease[2], while another study in China showed higher Sequential Organ Failure Assessment (SOFA) to be associated with in hospital mortality.[3] Grasselli *et al*., in a retrospective study conducted among 1,591 patients treated at one of the 72 hospitals of the COVID-19 Lombardy ICU network, showed lower median fraction of inspired oxygen (FiO_2) and higher partial pressure of oxygen (PaO_2)/ FiO_2 ratio in younger patients and those without hypertension, and higher mortality rates in older patients.[4]

With the increasing number of patients and limited resources available to accommodate them, there is a need for risk stratification tools to be developed to ensure better utilization of resources. Addressing this problem, the COVID GRAM risk score was developed in China to predict the occurrence of critical illness in hospitalized patients with COVID19.[5]

We conducted this study to assess the utility of the COVID GRAM risk score in patients presenting to a large tertiary care hospital in a developing country. The primary outcome of the study was accuracy of the COVID GRAM score to predict development of critical disease according to the criteria of the COVID-GRAM development and validation study.[5] Secondary outcomes were the accuracy of the use of the COVID GRAM score to predict development of severe and critical COVID-19 disease in patients with mild and moderate disease as per the WHO definition at admission.

MATERIAL AND METHODS

A retrospective observational cohort study was conducted at the COVID designated areas of a large tertiary care hospital in Karachi, Pakistan. Non-probability consecutive sampling technique was employed and a list of patients discharged from COVID designated areas of the hospital from the 1st of May to the 31st of July, 2020 was extracted. Laboratory confirmation of COVID-19 infection irrespective of clinical signs and symptoms was the case definition.[6] The Ethical Review Committee (ERC) of the University Hospital approved the study (Reference Number 2020-5102-14019). The need for informed consent was waived as only files and electronic health record were reviewed retrospectively. No identifiable information such as name, address, etc. was collected.

The inclusion criteria included all adult patients aged 18 years or older who were hospitalized with the diagnosis of COVID-19. The exclusion criteria included patients with incomplete records, patients with COVID-19 diagnosed by methods other than Reverse Transcription Polymerase Chain Reaction (RT-PCR) assay (Roche, Basel, Switzerland) and patients with suspected COVID-19 in which laboratory assessment was inconclusive. Demographic information such as age, gender, comorbidities, etc. and laboratory parameters such as CRP. LDH, D-dimer, etc. was collected by reviewing the medical record files and the electronic health records. The highest oxygen requirement was used along with the lowest PaO_2/ FiO_2 ratios within 24 hours of admission to the emergency department. Where ABG analysis was not available the PaO2 was estimated.[7] The initial laboratory values within 48 hours of admission to the emergency department and prior to development of critical illness were used. Data was collected using a pre-designed *pro forma.*

The COVID GRAM score was calculated for patients presenting without critical COVID-19 disease according to COVID GRAM study criteria at the time of admission. Patients progressing and those not progressing to critical disease after a minimum of 24 hours of admission to the emergency department were determined. Critical disease as per the COVID GRAM study criteria was defined as a composite of need of ICU admission, invasive ventilation or death.[5]

The severity of COVID-19 was also determined according to the WHO criteria[8] at the time of admission. According to the WHO, symptomatic patients meeting the case definition for COVID-19 without evidence of viral pneumonia or hypoxia are labelled as having mild disease. Those with clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) but no signs of severe pneumonia, including oxygen saturation (SpO2) ≥90% on room air are said to have moderate disease. Patients with clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) plus one of the following: respiratory rate >30 breaths/min; severe respiratory distress; or SpO2 <90% on room air, have severe disease. Critical disease is defined as the development of sepsis[9], septic shock[9] or acute respiratory distress syndrome (ARDS).[10]

Patients with mild and moderate COVID-19 disease according to the WHO criteria at admission and those who progressed to severe or critical disease after a minimum of 24 hours after admission to the emergency department were also noted.

In cases of patients who were readmitted, only the first admission was considered to control for hospital-acquired complications on readmission.

IBM Statistical package for the Social Sciences (SPSS) version 23.0 was used for data analysis. The frequency and percentage of qualitative variables were determined. The mean and standard deviation of quantitative variables was also determined. The Area under the Receiver Operator Curve (AUC) for the COVID GRAM risk score to predict development of critical illness was determined. Additionally, the AUC for the COVID GRAM risk score to predict development of severe or critical disease in patients with mild or moderate disease as per WHO criteria on admission was also determined. The Chi-Squared test was used to determine the relationship between categorical variables while the relationship between numerical and categorical values was determined using the independent sample t-test. For the purpose of logistic regression, WHO categories were dichotomized as mild/moderate and severe/critical disease. Univariate logistic regression was performed to identify factors associated with mortality 24 hours after admission and severe/critical disease as per WHO criteria on admission. Variables with a *p*-value <0.25 were included in the multivariable model. Multivariable logistic regression was performed to identify independent factors associated with mortality 24 hours after admission and severe/critical disease as per WHO criteria on admission. A p-value of <0.05 was considered to be significant with a confidence interval of 95%.

RESULTS

Out of 916 patients discharged from the COVID designated areas of the hospital, 581 patients were deemed eligible as per the inclusion criteria after review of medical record file and the electronic health record. Study outline is provided in figure-1.

The mean age and standard deviation of the study population was 56.3±14.8. 69.2% of patients were male while 30.8% were female. 65.2% of patients had one or more comorbidities. COVID GRAM scores were not significantly different between the genders. The most common comorbidities were hypertension (45.6%), diabetes mellitus (39.4%) and cardiovascular disease (18.1%).

The mean COVID GRAM score for the total study population was 136.9±51.8. When comparing COVID GRAM scores for patients that met COVID GRAM criteria for critical disease during admission versus those that did not, the mean COVID GRAM score of the former group was 183.2±80.7 versus 130.3±42.6 in the latter group. Similarly, patients with mild or moderate disease according to the WHO criteria had lower COVID GRAM scores compared to those with severe or critical disease at the time of admission. Table-1 represents characteristics of patients with mild/moderate and severe/critical disease at the time of admission while table 2.0 represents patients who developed critical illness as per COVID GRAM criteria[5] 24 hours after admission versus those who did not.

Length of hospital stay was significantly longer in those with higher COVID GRAM scores. Those who did not fulfil the criteria for critical disease were discharged from the hospital (93.1%) or left against medical advice/transferred to another facility (6.9%). 73.6% patients in the critically ill group died.

Categorical variables that were significant in patients that met COVID GRAM criteria for critical disease include the comorbid conditions of hypertension (*p*-value: 0.05), cardiovascular disease (*p*-value: <0.001), chronic kidney disease (*p*-value: 0.014) and malignancy (*p*-value: 0.036). Numerical variables that were significant include the COVID GRAM score, the SOFA score, Ferritin, LDH and CRP. Further details are provided in table 1.0 and 2.0. Out of 198 patients with mild or moderate disease according to the WHO criteria at the time of admission, 18 (9.1%) patients subsequently developed severe or critical disease. These patients had a longer length of hospital stay (9.8±5.4 versus 4.2±3.2 days, *p*-value <0.001).

The AUC of the COVID GRAM score to predict development of critical disease according to the COVID GRAM study criteria in the study population was 0.802 (95% confidence interval, 0.753–0.850) which was the primary outcome of the study. The AUC of the COVID GRAM score to predict development of severe or critical disease in patients with mild or moderate disease as per WHO criteria at the time of admission was 0.587 (95% confidence interval, 0.455–0.718) and was the secondary outcome. The ROC curves are displayed in figure-2.

On binary logistic multivariate regression analysis, it was found that the COVID GRAM score was a significant predictor of severe/critical disease as per the WHO criteria at the time of admission (*p*-value <0.001). It was also a significant predictor of mortality (*p*-value: 0.013) 24 hours after admission to the emergency department. Other significant predictors of mortality are displayed in table-3.

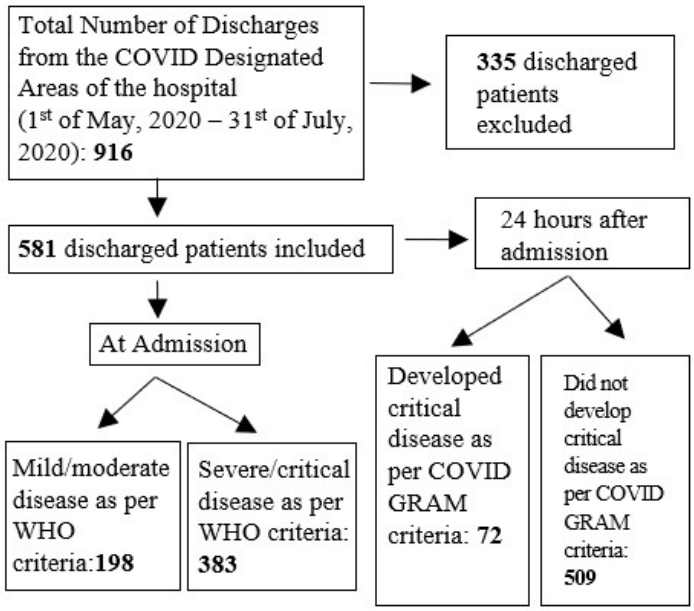

Figure-1: Study outline

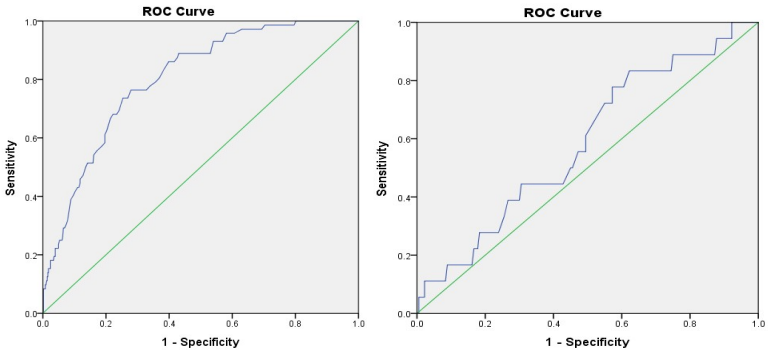

Figure-2: Area under the Receivr Operator

Curves (ROC) for the use of the COVID GRAM score to predict development of critical disease as per COVID GRAM criteria 24 hours after admission (a) and use of the COVID GRAM score to predict development of severe/critical disease as per WHO criteria 24 hours after admission in patients with mild/moderate disease at the time of admission (b)

Table-1: Characteristics of hospitalized patients who developed critical disease as per COVID GRAM study criteria during admission versus those that did not.

Variable	**Total** (Mean±SD/ n (%)	**Met COVID GRAM criteria for critical disease on Admission: Yes** (Mean±SD) / n (%)	**Met COVID GRAM criteria for critical disease of admission: No** (Mean±SD) / n (%)	***p*-value** (95% Confidence Interval)
Age	56.3±14.8	64.9±15.0	55.1±14.4	<0.001
Gender			0.298	
Male	402 (69.2%)	46 (63.9%)	356 (69.9%)	-
Female	179 (30.8%)	26 (36.1%)	153 (30.1%)	-
Number of co-morbidities			<0.001	
0	202 (34.8%)	11 (15.3%)	191 (37.5%)	-
1	161 (27.7%)	19 (26.4%)	142 (27.9%)	-
2	121 (20.8%)	21 (29.2%)	100 (19.7%)	-
3	71 (12.2%)	15 (20.8%)	56 (11.0%)	-
4	24 (4.1%)	6 (8.3%)	18 (3.5%)	-
5	2 (0.3%)	0 (0%)	2 (0.4%)	-
Number of days from symptom onset to admission	7.4±4.2	6.2±3.8	7.6±4.3	0.012
Length of Hospital Stay (Days)	7.3±5.5	13.2±9.0	6.4±4.2	<0.001
Outcome				
Discharged	492 (84.7%)	18 (25%)	474 (93.1%)	-
Expired	53 (9.1%)	53 (73.6%)	0 (0%)	-
Left Against Medical Advice or transferred to an outside hospital	36 (6.2%)	1 (1.4%)	35 (6.9%)	-
Days from symptom onset to outcome	14.6±6.9	19.4±10.1	13.9±6.0	<0.001
COVID GRAM Score	136.9±51.8	183.2±80.7	130.3±42.6	<0.001
SOFA Score	2.3±1.7	4.0±1.8	2.0±1.6	<0.001
Pa02 at room air (mmHg)	71.7±16.0	61.1±15.8	72.7±15.7	<0.001
Fi02 (%)	35±16	48±15	33±15	<0.001
P/F Ratio	295.7±120.4	210.7±100.4	307.8±118.2	<0.001
CRP (mg/L)	115.3±84.7	141.3±88.1	111.6±83.6	<0.001
Ferritin (ng/mL)	1052.4±1820.8	2057.4±4201.0	909.1±1067.2	0.026
LDH (I.U/L)	493.4±462.8	769.3±1194.0	454.4±181.7	0.029
Procalcitonin (ng/mL)	1.738±9.571	4.691±18.083	1.311±7.531	0.130
D-Dimer (mg/L)	2.9±6.1	4.4±6.8	2.7±6.0	0.070
INR	1.1±0.3	1.2±0.4	1.1±0.3	0.205
Direct Bilirubin (mg/dL)	0.3±0.7	0.6±1.4	0.3±0.5	0.105
SGPT (IU/L)	67.8±85.2	89.4±152.0	64.7±70.6	0.178
SGOT (IU/L)	77.2±145.5	138.6±360.5	68.5±73.5	0.104
NLR	7.9±8.2	11.1±11.7	7.4±7.5	0.011
Required HDU Admission	356 (61.3%)	69 (95.8%)	287 (56.4%)	<0.001
Required ICU admission	37 (6.4%)	37 (51.4%)	0 (0%)	<0.001

SOFA: Sequential Organ Failure Assessment. PaO2: Partial pressure of oxygen, FiO2: Fraction of inspired oxygen. P/F Ratio: Partial pressure of oxygen / Fraction of inspired oxygen. CRP: C-Reactive Protein. LDH: Lactate Dehydrogenase. ALT: Alanine aminotransferase. AST: Aspartate aminotransferase. NLR: Neutrophil: Lymphocyte Ratio HDU: High Dependency Unit. ICU: Intensive Care Unit.

Table-2: Characteristics of hospitalized patients who developed critical disease as per COVID GRAM study criteria 24 hours after admission versus those that did not.

Variable	**Total** (Mean ± Standard Deviation/ n (%)	**Met COVID GRAM criteria for critical disease 24 hours after admission: Yes** (Mean ± Standard Deviation) / n (%)	**Met COVID GRAM criteria for critical disease 24 hours after admission: No** (Mean ± Standard Deviation) / n (%)	***p*-value** (95% Confidence Interval)
Age (years)	56.3 ± 14.8	64.9 ± 15.0	55.1 ± 14.4	<0.001
Gender				0.298
Male	402 (69.2%)	269 (70.2%)	133 (67.2%)	
Female	179 (21.8%)	114 (29.8%)	65 (32.8%)	
Number of co-morbidities				<0.001
0	202 (34.8%)	11 (15.3%)	191 (37.5%)	
1	161 (27.7%)	19 (26.4%)	142 (27.9%)	
2	121 (20.8%)	21 (29.2%)	100 (19.7%)	
3	71 (12.2%)	15 (20.8%)	56 (11.0%)	
4	24 (4.1%)	6 (8.3%)	18 (3.5%)	
5	2 (0.3%)	0 (0%)	2 (0.4%)	
Number of days from symptom onset to Admission	7.4 ± 4.2	6.2 ± 3.8	7.6 ± 4.3	0.012
Length of Hospital Stay (Days)	7.3 ± 5.5	13.2 ± 9.0	6.4 ± 4.2	<0.001
Outcome				
Discharged	492 (84.7%)	18 (25%)	474 (93.1%)	
Expired	53 (9.1%)	53 (73.6%)	0 (0%)	
Left Against Medical Advice or transferred to an outside hospital	36 (6.2%)	1 (1.4%)	35 (6.9%)	
Days from symptom onset to outcome	14.6 ± 6.9	19.4 ± 10.1	13.9 ± 6.0	<0.001
COVID GRAM Score	136.9 ± 51.8	183.2 ± 80.7	130.3 ± 42.6	<0.001
SOFA Score	2.3 ± 1.7	4.0 ± 1.8	2.0 ± 1.6	<0.001
Pa02 at room air (mmHg)	71.7 ± 16.0	61.1 ± 15.8	72.7 ± 15.7	<0.001
Fi02 (%)	35 ± 16	48 ± 15	33 ± 15	<0.001
P/F Ratio	295.7 ± 120.4	210.7 ± 100.4	307.8 ± 118.2	<0.001
CRP (mg/L)	115.3 ± 84.7	141.3 ± 88.1	111.6 ± 83.6	<0.001
Ferritin (ng/mL)	1052.4 ± 1820.8	2057.4 ± 4201.0	909.1 ± 1067.2	0.026
LDH (I.U/L)	493.4 ± 462.8	769.3 ± 1194.0	454.4 ± 181.7	0.029
Procalcitonin (ng/mL)	1.738 ± 9.571	4.691 ± 18.083	1.311 ± 7.531	0.130
D-Dimer (mg/L)	2.9 ± 6.1	4.4 ± 6.8	2.7 ± 6.0	0.070
INR	1.1 ± 0.3	1.2 ± 0.4	1.1 ± 0.3	0.205
Direct Bilirubin (mg/dL)	0.3 ± 0.7	0.6 ± 1.4	0.3 ± 0.5	0.105
ALT (IU/L)	67.8 ± 85.2	89.4 ± 152.0	64.7 ± 70.6	0.178
AST (IU/L)	77.2 ± 145.5	138.6 ± 360.5	68.5 ± 73.5	0.104
NLR	7.9 ± 8.2	11.1 ± 11.7	7.4 ± 7.5	0.011
Required HDU Admission	356 (61.3%)	69 (95.8%)	287 (56.4%)	<0.001
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SOFA: Sequential Organ Failure Assessment. PaO2: Partial pressure of oxygen, FiO2: Fraction of inspired oxygen. P/F Ratio: Partial pressure of oxygen / Fraction of inspired oxygen. CRP: C-Reactive Protein. LDH: Lactate Dehydrogenase. ALT: Alanine aminotransferase. AST: Aspartate aminotransferase. NLR: Neutrophil: Lymphocyte Ratio HDU: High Dependency Unit. ICU: Intensive Care Unit

Table-3: Binary logistic multivariable regression analysis to find predictors of severe/critical disease as per WHO criteria on admission and mortality 24 hours after admission. CRP: C - reactive protein. ICU: Intensive Care Unit.

Variable	Adjusted odds Ratio	*p*-value (95% confidence interval)
Severe/Critical disease as per WHO criteria on admission		
COVID GRAM score on admission	1.049	<0.001
CRP	1.005	0.009
Mortality 24 hours after admission		
COVID GRAM score on admission	1.011	0.013
SOFA score on admission	1.558	0.004
Need of ICU admission	13.266	<0.001

DISCUSSION

In this study we assessed the use of the COVID GRAM score to predict development of critical disease in patients with COVID19 presenting to a tertiary care hospital in a developing country. The AUC achieved for the COVID GRAM score in our study population was 0.802 (95% confidence interval, 0.753–0.850) which is lower compared to the 0.88 achieved in the study by Liang et al. in the development and validation cohorts. In their study however the AUC in the developmental cohort for patients in the Hubei province was 0.87 while it was 0.82 for patients outside of this area.[5]

Other risk scores have also now been developed in other countries. The AUC for the COVID GRAM score when used in Mexico (0.78 and 0.77)[11] and the UK (0.706)[12] also showed lower AUC values than the study by Liang *et al*.[5]

In our study the majority of patients that came to the hospital had severe/critical disease as per WHO criteria at the time of admission (65.9%). 61.3% required admission to the HDU at some point during the hospital stay while 6.4% of patients required transfer to the ICU 24 hours after admission to the emergency department. In our study, requirement for HDU/ICU admission in patients presenting with severe/critical disease as per the WHO criteria was around 4 times higher than in those patients presenting with mild/moderate disease (Table-2). These facilities are especially limited in the developing world making risk assessment tools even more relevant and valuable. To our knowledge this is the first study to explore the association of the COVID GRAM score with the WHO classification of severity of COVID-19 illness.

Consistent with previous studies, older patients and those with comorbidities were the most likely to develop critical illness.[2] It is imperative that this patient population be protected by others around them through practices of wearing face masks, social distancing[13] and hand hygiene.[14] Also they should be at the forefront of those to receive vaccination for COVID19 as it is made available.

The main limitation of our study is a small sample size while a large majority of our patients who require non-invasive ventilation (NIV) are managed outside the ICU.

As the world is engulfed in the second wave of COVID-19 and with the promise of vaccines emerging as a ray of hope, risk assessment tools are still useful to ensure optimal allocation and adequate utilization of limited resources especially in the developing world.

CONCLUSION

The AUC for the COVID gram score to predict critical illness in the study population was 0.802 (95% confidence interval, 0.753–0.850). Need of ICU care during hospitalization, SOFA score on admission and COVID GRAM score on admission were significant predictors of mortality 24 hours after admission on multivariable binary logistic regression analysis while the COVID GRAM score and CRP on admission were significant predictors of severe/critical disease as per WHO criteria on admission.

AUTHORS' CONTRIBUTION

HJ: Conceptualization, study design, data collection, data analysis and manuscript writing. AA: conceptualization, study design, project administration, data analysis, review and editing. RSM: Data analysis, review and editing. BJ: Review and editing.

REFERENCES

1. WHO. Rolling updates on coronavirus disease (COVID-19). [Internet]. [cited 2020 Jun 13]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen
2. Feng Y, Ling Y, Bai T, Xie Y, Huang J, Li J, *et al*. COVID-19 with different severities: a multicenter study of clinical features. Am J Respir Crit Care Med 2020;201(11):1380–8.
3. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, *et al*. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395(10229):1054–62.
4. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, *et al*. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. JAMA 2020;323(16):1574–81.
5. Liang W, Liang H, Ou L, Chen B, Chen A, Li C, *et al*. Development and validation of a clinical risk score to predict

the occurrence of critical illness in hospitalized patients with COVID-19. JAMA Intern Med 2020;180(8):1081–9.
6. WHO. Coronavirus disease (COVID-2019) situation reports. [Internet]. [cited 2020 Jun 13]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports
7. Madan A. Correlation between the levels of SpO_2 and PaO_2. Lung India 2017;34(3):307–8.
8. WHO. Clinical management of COVID-19. [Internet]. [cited 2020 Jun 13]. Available from: https://www.who.int/publications/i/item/clinical-management-of-covid-19
9. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, *et al*. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016;315(8):801–10.
10. Ferguson ND, Fan E, Camporota L, Antonelli M, Anzueto A, Beale R, *et al*. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. Intensive Care Med 2012;38(10):1573–82.
11. Mejía-Vilet JM, Córdova-Sánchez BM, Fernández-Camargo DA, Méndez-Pérez RA, Morales-Buenrostro LE, Hernández-Gilsoul T, *et al*. A Risk Score to Predict Admission to Intensive Care Unit in Patients With COVID-19: The ABC-GOALS Score. Salud Publica Mex 2021;63(1):1–11.
12. Knight SR, Ho A, Pius R, Buchan I, Carson G, Drake TM, *et al*. Risk stratification of patients admitted to hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: development and validation of the 4C Mortality Score. BMJ 2020;370:m3339.
13. Andersen M. Early evidence on social distancing in response to COVID-19 in the United States. [Internet]. [cited 2020 Jun 13]. Available from: https://poseidon01.ssrn.com/delivery.php?ID=423027122029098005116017096098082085055056033007026070025020074117106120081090095030097010120030123038049121098082068008027111016054063082050068119090113112013119120042042047067009022001121026125002022073023113107122097079092100073090090072027072064029&EXT=pdf&INDEX=TRUE
14. Huang GK, Stewardson AJ, Grayson ML. Back to basics: hand hygiene and isolation. Curr Opin Infect Dis 2014;27(4):379.

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