

Decreased PRESET-Score corresponds with improved survival in COVID-19 veno-venous extracorporeal membrane oxygenation

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Abstract

Introduction: The PREdiction of Survival on ECMO Therapy Score (PRESET-Score) predicts mortality while on veno-venous extracorporeal membrane oxygenation (VV ECMO) for acute respiratory distress syndrome. The aim of our study was to assess the association between PRESET-Score and survival in a large COVID-19 VV ECMO cohort.

Methods: This was a single-center retrospective study of COVID-19 VV ECMO patients from 15 March 2020, to 30 November 2021. Univariable and Multivariable analyses were performed to assess patient survival and score differences. Results: A total of 105 patients were included in our analysis with a mean PRESET-Score of 6.74. Overall survival was 65.71%. The mean PRESET-Score was significantly lower in the survivor group (6.03 vs 8.11, p < 0.001). Patients with a PRESET-Score less than or equal to six had improved survival compared to those with a PRESET-Score greater than or equal to 8 (97.7% vs. 32.5%, p < 0.001). In a multivariable logistic regression, a lower PRESET-Score was also predictive of survival (OR 2.84, 95% CI 1.75, 4.63, p < 0.001).

Conclusion: We demonstrate that lower PRESET scores are associated with improved survival. The utilization of this validated, quantifiable, and objective scoring system to help identify COVID-19 patients with the greatest potential to benefit from VV-ECMO appears feasible. The incorporation of the PRESET-Score into institutional ECMO candidacy guidelines can help insure and improve access of this limited healthcare resource to all critically ill patients.

Keywords

circulatory support, circulatory temporary support, extracorporeal membrane oxygenation, COVID-19

Introduction

SARS-CoV-2 (COVID-19) commonly causes respiratory symptoms and in the most severe cases, acute respiratory distress syndrome (ARDS).¹ Though there are some unique COVID-19 treatments, the ARDS illness associated with COVID-19 is largely treated similarly to other non-COVID-19 disease processes with lung protective strategies, paralysis, prone positioning, and in the most severe cases, veno-venous extracorporeal membrane oxygenation (VV ECMO).¹

VV ECMO improves outcomes in patients with ARDS² likely by facilitating improved gas exchange and thus allowing the delivery of lung protective ventilation and minimization of secondary lung injury.³ Over the

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past 20 years, improvements in ECMO technology have made it more available to patients globally.⁴ As the use of VV ECMO has become more prevalent, so has the use of scoring systems to help identify which patients may most benefit from its use.

One such system, the PREdiction of Survival on ECMO Therapy Score (PRESET-Score) utilizes several extrapulmonary factors pre-ECMO including mean arterial pressure (MAP), pH, lactic acid, platelet count, and hospital length of stay (LOS) to predict intensive care unit (ICU) mortality on VV ECMO.⁵ While the PRESET-Score was developed prior to the COVID-19 global pandemic, in one recent study of 40 COVID-19 patients, a lower PRESET-Score was associated with improved survival.⁶ This prompted the incorporation of the PRESET-Score as part of COVID-19 VV ECMO patient evaluation at our institution.⁶

To better identify patients with COVID-19 ARDS who could benefit most from VV ECMO, we studied the association between PRESET-Score and survival. We also studied patient characteristics and survival pre- and post-implementation of the PRESET-Score as part of a multi-disciplinary VV ECMO consultation process. We hypothesize that lower PRESET scores will be associated with improved survival, suggesting that this objective scoring system be included in ECMO candidacy guidelines.

Methods

Study design

This is a single center, retrospective chart review. Our study was approved by the University of Maryland School of Medicine Institutional Review Board (HP-00099380) and the need for written consent was waived.

Patient selection

All COVID-19 ARDS VV ECMO patients from 15 March 2020 to 30 November 2021 were screened for inclusion in our study. Inclusions criteria included: age greater than or equal to 18 years old, VV ECMO without alternate ECMO cannulation strategy (veno-arterial or veno-veno-artial), and cannulated and managed at our institution.

COVID-19 veno-venous extracorporeal membrane oxygenation candidate criteria

Our institution utilizes a multi-disciplinary approach for VV ECMO candidate selection. On each referral call, an

intensivist from the Critical Care Resuscitation Unit (CCRU),⁷ an intensivist from the Lung Rescue Unit (LRU),⁸ and a cardiac surgeon discuss the case and apply institutional guidelines for selection. The CCRU is a receiving intensive care unit (ICU) for the R Adams Cowley Shock Trauma Center and the University of Maryland Medical Center and the LRU is a dedicated VV ECMO ICU.

Throughout the pandemic, ECMO candidacy guidelines were evidence based.^{9,10} Criteria for consideration for VV ECMO included the following: hypercapnia (partial pressure of carbon dioxide (PaCO₂) > 60 mmHg with a pH < 7.25); inability to ventilate adequately with plateau pressure of 30 cm H₂O or less; and severe hypoxemia (ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO₂/FiO₂) < 50 mmHg with FiO₂ > 80% for >3 h, or PaO₂/FiO₂ ratio <80 mmHg with FiO₂ > 80% for >6 h) despite maximal ventilatory support and use of adjunctive therapies such as prone positioning, neuromuscular blockade, and inhaled pulmonary vasodilators.

From March 15 to 11 May 2020, initial COVID-19 VV ECMO institutional guidelines were used: age (<60), ventilator days (≤ 10), and body mass index (BMI) $(\leq 50 \text{ kg/m}^2)$. Twenty-four patients were selected and included in this analysis during this criteria period. From 12 May 2020, through the study period, age recommendations for consideration (≤55), ventilator days (≤7), and BMI (≤40) decreased. Recommended consideration of co-morbidities, end organ function, laboratory values, and ventilator settings did not change throughout the pandemic. All criteria were considered relative, and each case was discussed individually by the multi-disciplinary team so patients falling outside the recommendations could and were still selected. There were no specific co-morbidities that would be considered an absolute contraindication, however, prognosis with each comorbidity was considered and discussed on an individual basis. When analyzing pre-criteria change (n = 24) and post criteria change (n = 31) characteristics and scoring systems of the two groups (all prior to the PRESET-Score addition), no differences in groups were observed (Supplemental Table 1). When analyzing frequency distribution of age (p = 0.51), BMI (p = 0.4), and ventilator days (p = 0.45), characteristics between the groups were also similar. This indicates that despite the recommendation changes, there was not a significant difference in these characteristics between groups.

The PRESET-Score is one scoring system used by our institution to evaluate patient survival on VV ECMO (Supplemental Table 2). After initial institutional data suggested that patients with lower PRESET scores had better outcomes,⁶ from 26 November 2020 onward, the PRESET-

Score was used as part of our evaluation process. There was no absolute PRESET score that would preclude a patient from consideration for VV ECMO.

Data storage and analysis

Study data were collected and managed using Research Electronic Data Capture (REDCap) tools hosted at the University of Maryland.^{11,12} Demographics, pre-ECMO data, and patient outcomes were analyzed. The primary outcome was survival to hospital discharge. Our secondary outcome was patient survival at discharge pre- and post-implementation (26 November 2020) of the PRESET-Score as part of the ECMO screening process. All scoring systems were calculated pre-ECMO cannulation.

Data were analyzed with descriptive statistics. Parametric or nonparametric statistics were used based on the nature of the data. Normality was assessed with the Shapiro-Wilk test, and examination of stem-and-leaf as well as q-q plots. The student's t-test was used to assess differences with parametric continuous data and the Kruskall-Wallis and Wilcoxon rank sum tests were used to analyze nonparametric data. Normally distributed data was presented with mean and standard deviation (SD) while nonnormally distributed data was presented with median and quartiles (Q1-Q3). Chi square tests were used to analyze categorical data. All tests were two-tailed and a p value of <0.05 was used to define statistical significance.

Logistic regression, with calculation of robust standard errors, was performed after variables were selected based on Akaike's information criterion (AIC). Regression diagnostics were performed including a link test to assure proper model specification and the Hosmer-Lemeshow chi-square goodness-of-fit test. Model fit (p = 0.48) and specification were confirmed. Deviance residuals and Pearson residuals as well as leverage and influence were also assessed to confirm the required assumptions for the logistic regression model. All tests were performed in Stata version 17 (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC) and GraphPad Prism 7.0 for Mac (GraphPad Software, La Jolla, CA).

Results

Demographics and characteristics

One hundred and five COVID-19 patients, who met our inclusion criteria, were cannulated for VV ECMO during the study period. Pre-ECMO characteristics were analyzed for survivors (n = 69) and non-survivors (n = 36) (Table 1). There was a lower percentage of males in the survivor group (57.95% vs. 91.67%, p < 0.001). Age,

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BMI, ventilator days, and P/F ratio were similar between survivors and non-survivors. A significantly higher percentage of survivors received steroids prior to VV ECMO initiation (88.41% vs. 66.67%, p = 0.01). Scoring systems were then analyzed between survivors and nonsurvivors. The PRESET-Score was significantly lower in the survivor group (6.03 vs 8.11, p < 0.001). The Respiratory ECMO Survival Prediction (RESP) score was significantly higher in the survivor group (4.17 vs 3.08, p = 0.006).

When comparing the demographics and characteristics of the pre- (n = 55) and post-implementation (n = 50) groups, there was no difference in age, percentage of males, BMI, ventilator days, P/F ratio, Sequential Organ Failure Assessment (SOFA), RESP, or PRESET scores (Table 2). In the post-implementation group, the Simplified Acute Physiology (SAPS II) score was significantly higher (41.43 vs 50.86, p < 0.001).

Unadjusted and adjusted analysis of the PRESET-Score and association with survival

Survival percentages were analyzed for all PRESET scores. Patients with a PRESET-Score less than or equal to six had improved survival compared to those with a PRESET-Score greater than or equal to 8 (97.7% vs. 32.5%, p < 0.001). There was a significant decrease in survival from a PRESET-Score of 6-7 (100% vs. 63.6%, p = 0.01). In addition, there was a further significant drop in survival from a PRESET-Score of 7-8 (63.6% vs. 33.3%, p = 0.04). Probability of survival with 95% confidence bands decreased as PRESET-Score increased (Figure 1). A receiver operator characteristic (ROC) curve was constructed with an area under the curve (AUC) of 0.84 (95% CI 0.76-0.91). When comparing survival between patients with a PRESET score less than or equal to 6, equal to 7, and greater than or equal to 8, a Kaplan-Meier survival curve again demonstrated decreased survival in patients with higher PRESET scores (Mantel-Cox log-rank test p < 0.001) (Figure 2).

A multivariable logistic regression analysis was then performed using mortality as the dependent variable. Female sex was independently associated with improved survival (OR 0.07, 95% CI 0.01, 0.37, p = 0.002). Increased PRESET-Score (OR 2.84, 95% CI 1.75, 4.63, p <0.001) was associated with decreased survival. All other values including age, BMI, scoring systems, and therapies pre-ECMO did not demonstrate association with survival. Variance inflation factor was less than 10.

Comparison of the PRESET-Score and Outcomes in the Pre- and Post-Implementation Groups

There was no observed difference in hours on ECMO and LOS (days) between pre-implementation of the PRESET-Score and post-implementation (Table 2).

	All patients ($n = 105$)	Survivors $(n = 69)$	Non-survivors ($n = 36$)	þ value
Age median (IQR)	43 (35–50)	42 (34–50)	43.5 (36.5–50.5)	0.60
Male sex- n (%)	73 (69.52)	40 (57.97)	33 (91.67)	<0.001
Co morbidities- n (%)				
Smoker	4 (3.81)	2 (2.9)	2 (5.56)	0.50
Asthma/COPD	9 (8.57)	9 (13.04)	0 (0)	
DM	19 (18.10)	10 (14.49)	9 (25)	0.18
Substance abuse	2 (1.90)	I (I.45)	I (2.78)	0.64
Perinatal	4 (3.81)	3 (4.35)	I (2.78)	0.69
Pre-ECMO therapies- n (%)				
Paralysis	101 (96.19)	65 (94.2)	36 (100)	0.14
Prone position	71 (67.62)	46 (66.67)	25 (69.44)	0.77
Inhaled pulmonary vasodilator	15 (14.29)	9 (13.04)	6 (16.67)	0.61
Steroids	85 (80.95)	61 (88.41)	24 (66.67)	0.01
Meduri (13)	24 (28.24)	17 (27.87)	7 (29.17)	0.82
Inflammatory (14)	54 (63.53)	40 (65.57)	14 (58.33)	0.53
Stress	7 (8.24)	4 (6.56)	3 (12.50)	0.37
Convalescent plasma	37 (35.24)	25 (36.23)	12 (33.33)	0.77
Remdesivir	65 (61.9)	45 (65.22)	20 (55.56)	0.33
Monoclonal antibody	30 (28.57)	18 (26.1)	12 (33.33)	0.44
BMI median (IQR)	34.5 (28.7–40.5)	36 (29–42)	33.15 (28.2–39.59)	0.67
Ventilator days median (IQR)	2 (1-5)	2 (1–5)	3 (1-4)	0.62
P/F Ratio median (IQR)	73 (60–84)	71 (60–86)	74 (59.5–83)	0.77
SOFA mean (SD)	10.48 (2)	10.17 (2)	11.06 (2)	0.06
RESP mean (SD)	3.8 (2)	4.17 (2)	3.08 (2)	0.006
SAPS II mean (SD)	46.02 (12)	44.51 (12)	48.92 (11)	0.08
PRESET mean (SD)	6.74 (2)	6.03 (2)	8.11 (1)	<0.001
Survival- n (%)	69 (65.71)	_	_	

Table I. Patient demographics and characteristics of COVID-19 VV EMO patients analyzed by survivors and non-survivors.

Meduri steroid protocol: Methylprednisolone dosed according to Meduri et al.¹³ Inflammatory steroid dosing: Dexamethasone according to the DEXA-ARDS study¹⁴ Stress dose steroid dosing: Hydrocortisone 50 mg every 6 h with weaning timeframe based on clinician discretion. BMI: Body mass index; CAD: Coronary artery disease; COPD: Chronic Obstructive Pulmonary Disease; CHF: Congestive heart failure: DM: Diabetes

mellitus; HIV: Human Immunodeficiency Virus; IQR: Interquartile Range; LOS: Length of Stay; P/F: PaO2/FiO2; PRESET: PREdiction of Survival on ECMO Therapy; RESP: Respiratory ECMO Survival Prediction; SOFA: Sequential Organ Failure Assessment; SAPS II: Simplified Acute Physiology Score; SD: Standard deviation; VV ECMO: Veno-venous extracorporeal membrane oxygenation.

There was no statistically significant difference in survival between the pre-and post-implementation groups (60% vs. 72%, p = 0.2). The mean PRESET-Score was lower in the post-implementation group, but this did not reach statistical significance (6.96 vs 6.5, p = 0.23). However, significantly more patients with PRESET scores less than or equal to six were selected in the post-implementation group (30.9%, 52%, p = 0.03). Frequency distribution was used to illustrate the PRESET score of the ECMO patients in both groups (Figure 3).

Discussion

PRESET-Score as the preferred scoring system for screening COVID-19 patients for VV ECMO

Our data demonstrate that lower PRESET scores correspond to improved outcomes for COVID-19 patients cannulated for VV ECMO(5). In this study, we again demonstrated with a larger cohort that lower PRESET corresponded to improved survival. In patients with scores less than or equal to 6, we observed a 97.7% survival to discharge. However, with scores 8 or greater, survival decreased below 40%.

After initial data indicated that PRESET scores less than or equal to six were associated with improved outcomes in our COVID-19 ARDS population,⁶ we began formally using the PRESET-Score as part of our multi-disciplinary patient screening process. Though we did not have absolute cutoffs in patient consideration based on solely PRESET-Score, values less than or equal to six were considered favorably and values of seven were also acceptable in the context of other screening guidelines. Patients with PRESET scores greater than or equal to eight were still cannulated on a case-by-case basis based on guidelines and multi-disciplinary

	Pre-implementation $(n = 55)$	Post-implementation $(n = 50)$	þ value
Age median (IQR)	43 (37–52)	42.5 (31–49)	0.26
Male sex- n (%)	42 (76.36)	31 (62.00)	0.11
Co morbidities- n (%)			
Smoker	3 (5.45)	I (2.00)	0.36
Asthma/COPD	4 (7.27)	5 (10.00)	0.62
DM	13 (23.64)	6 (12.00)	0.12
Substance abuse	I (I.82)	I (2.00)	0.95
Perinatal	l (l.82)	3 (6.00)	0.26
BMI median (IQR)	34 (26–40)	36.01 (31–43)	0.41
Ventilator days median (IQR)	2 (1-4)	2 (1-5)	0.88
P/F Ratio median (IQR)	68 (54–79)	77 (65–96)	0.26
SOFA mean (SD)	10.22 (3)	10.76 (2)	0.23
RESP mean (SD)	3.78 (2)	3.82 (2)	0.92
SAPS II mean (SD)	41.43 (12)	50.86 (10)	<0.001
PRESET mean (SD)	6.96 (2)	6.50 (2)	0.23
≤6 (n) (%)	17 (30.90)	26 (52.00)	0.03
Hours on ECMO median (IQR)	648 (480–1417)	791.5 (444–1464)	0.98
Hospital LOS in days median (IQR)	46 (31–69)	57 (35–88)	0.11
Survival- n (%)	33 (60)	36 (72)	0.2

Table 2. Characteristics and demographics of patients pre- and post-implementation of PRESET as part of the COVID-19 VV ECMO candidate screening process (26 November 2020).

BMI: Body mass index; CAD: Coronary artery disease; COPD: Chronic Obstructive Pulmonary Disease; CHF: Congestive heart failure: DM: Diabetes mellitus; HIV: Human Immunodeficiency Virus; IQR: Interquartile Range; LOS: Length of Stay; P/F: PaO₂/FiO₂; PRESET: PREdiction of Survival on ECMO Therapy; RESP: Respiratory ECMO Survival Prediction; SOFA: Sequential Organ Failure Assessment; SAPS II: Simplified Acute Physiology Score; SD: Standard deviation; VV ECMO: Veno-venous extracorporeal membrane oxygenation.



Figure 1. Probability of survival in COVID-19 patients on VV ECMO by PRESET-Score (a) and frequency distribution of survivors and non-survivors by PRESET-Score (b). (a) Probability of survival is on the Y axis with PRESET-Score located on the X axis shaded area represents 95% confidence bands, (b) Number of occurrences is on the Y axis and PRESET-Score is on the X axis. survivors and non-survivors are delineated by the legend. PRESET: PREdiction of Survival on ECMO Therapy; VV ECMO: Veno-venous extracorporeal membrane oxygenation.

physician discussion. After implementation of PRESET as part of screening, more patients had PRESET scores less than or equal to six indicating that we were selecting patients with lower scores for VV ECMO. When comparing pre- and post-implementation groups, there was no significant difference seen in survival rates.

In our screening process, the PRESET-Score seems more useful in selecting patients than other scoring systems. In this study, we observed that SAPS II was significantly higher in the post-implementation group suggesting that this group had decreased likelihood of survival,¹⁵ which was contrary to our findings. There was also no difference in survivors and non-survivors' SAPS II scores. We do not specifically use the RESP score as part of our screening, however, the criteria within the score are routinely collected and considered as part of our multi-disciplinary process. A greater RESP



Figure 2. Kaplan-Meier survival curve for COVID-19 VV ECMO patients based on PRESET-Score. probability of survival as a percentage is located on the Y axis hospital length of stay is represented on the X axis PRESET score categories are analyzed as less than or equal to 6, equal to 7, and greater than or equal to 8. Patients with higher PRESET scores had lower survival rates. PRESET: PREdiction of Survival on ECMO Therapy; VV ECMO: Veno-venous extracorporeal membrane oxygenation.



Figure 3. Histogram showing PRESET-Score frequency distribution pre-implementation (a) and post-implementation (b). More patients with a PRESET score less than or equal to six were selected post-implementation of the PRESET-Score as part of a multi-disciplinary screening process for VV ECMO cannulation in COVID-19. PRESET: PREdiction of Survival on ECMO Therapy; VV ECMO: Venovenous extracorporeal membrane oxygenation.

score would support improved survival, however, in our logistic regression, RESP score was not significant in predicting survival. In another recent study, the RESP score was also found to be a poor predictor of COVID-19 VV ECMO outcomes.¹⁶ There may be some bias in that we use the PRESET-Score specifically as part of our VV ECMO candidate screening, however, we routinely collect information used in other scores which were not observed as associated with survival in our study. This

indicates that the PRESET-Score is valuable when evaluating COVID-19 patients for VV ECMO.

The importance of extrapulmonary variables in the PRESET-Score

The PRESET-Score was initially developed prior to the COVID-19 pandemic to assist in identifying patients who would most benefit from VV ECMO(5). The variables used

in this score are typically readily available for most patients and the score has been both internally and externally validated in the non-COVID-19 population.¹⁷

Interestingly, the PRESET-Score does not include pulmonary variables. Hypotension, thrombocytopenia, acidosis, elevated lactate, and prolonged hospital stay have all been shown in the COVID-19 and non-COVID-19 populations to increase the risk of mortality.^{18–26} Perhaps, since patients are being considered for VV ECMO, all patients have severe pulmonary disease and predicting survival has more to do with the severity of these extrapulmonary variables.¹⁷ This was demonstrated in our study as both survivors and non-survivors had severe ARDS, as evidence by similar P/F ratios. Larger cohorts from multiple centers will be beneficial to determine if our findings are broadly applicable to other centers.

Limitations

There are several limitations to our work and the use of the PRESET-Score in COVID-19 patients. First, no data on COVID-19 variants were available during this study. Different variants of SARS-CoV-2 have been reported to be associated with variable mortality and multiorgan dysfunction.²⁷ Second, we did not have specific data about changes in COVID-19 VV ECMO patient management practice between the pre- and post-implementation groups. During this time, the understanding of how to treat and manage these patients was rapidly evolving and some of the individual treatments were based on clinician practice patterns. Though overall, the patient characteristics were similar pre-cannulation, given the length of time these patients typically required VV ECMO, there is certainly the possibility we are missing management confounders in our study. Third, the original PRESET-Score did not include COVID-19 patients when it was developed, internally, and externally validated.⁵ When applying this score to our COVID-19 population, we externally validated the score in our COVID-19 patient population but the applicability to other institutions could be variable. Further internal and external validation of the score in the COVID-19 patient population should be studied. Fourth, some of the other scoring systems share variables that might have led to collinearity and confounding (i.e. both the SOFA score and PRESET-Score include platelets and blood pressure; the RESP score includes bicarbonate use as a marker of acidemia). While we did not detect any significant covariance when constructing our regression model, it is possible that effect modification might have been present. Fifth, our recommended criteria for VV ECMO candidacy did change during the pandemic and prior to the initiation of the PRESET-Score as part of screening. When we analyzed patients pre- and post-change in the pre-implementation group, we found no difference in age, BMI, or ventilator

days. Scoring systems were also similar between the groups. This indicates that though our recommended criteria did change, our selection of candidates remained similar during this period. This is likely because though we had guidelines for selection, each case was decided by a multi-disciplinary group on an individual basis so candidates could fall outside our guidelines. Sixth, we have limited access to PRESET scores in patients declined for transfer that would have fallen in the pre-implementation group. This is because this data was not collected routinely on the transfer calls preimplementation of the score as part of our screening process. This data was collected for all post-implementation VV ECMO transfer consults; however, the data was used as part of our selection process by that point so could lead to some selection bias in the post-implementation group. Finally, for mortality assessment between pre- and post-implementation groups, post hoc sample size calculations were performed to assess statistical power for detecting associations between implementation groups and survival. Using a Wald test for detecting a 10% difference in survival we estimate we require approximately 126 patients. Thus, our study was underpowered to detect a mortality difference between these groups. Multicenter studies with larger cohorts will be beneficial to determine the utility of the PRESET-Score across institutions with various practice patterns and would further validate use of the PRESET-Score in COVID-19 VV ECMO screening.

Conclusions

We demonstrate that lower PRESET scores are associated with improved survival. The utilization of this validated, quantifiable, and objective scoring system to help identify COVID-19 patients with the greatest potential to benefit from VV ECMO appears feasible. The incorporation of the PRESET-Score into institutional ECMO candidacy guidelines can help insure and improve access of this limited healthcare resource to all critically ill patients.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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