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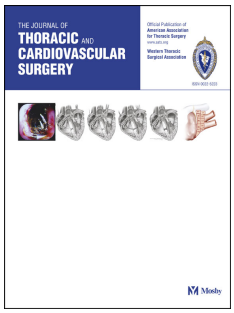

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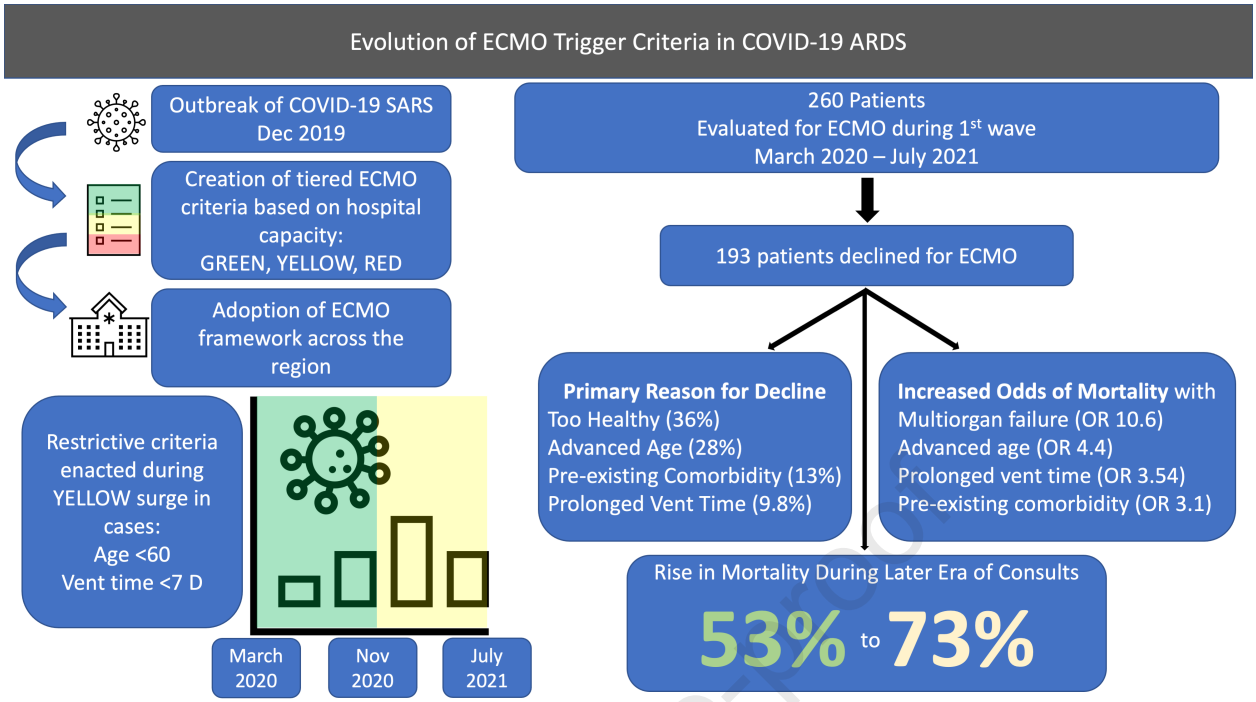

Evolution of ECMO Trigger Criteria in COVID-19 ARDS

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Glossary

ARDS – Acute respiratory distress syndrome

BiPAP – Bilevel positive airway pressure

COVID-19 – Coronavirus 2019 (SARS-COV2 virus)

CPAP- Continuous positive airway pressure

ECMO – Extracorporeal membrane oxygenation

ECLS – Extracorporeal life support

EHR – Electronic health record

HHFNC – Heated high flow nasal cannula

IPR – Inpatient rehabilitation

LTAC – Long term acute care facility

PaCO2 – Partial pressure of carbon dioxide

PaO2 – Partial pressure of oxygen

P/F ratio – PaO2:FiO2 ratio

RT-PCR – Reverse transcription positive chain reaction

VA-ECMO – Veno-arterial ECMO

VV-ECMO – Veno-venous ECMO

Central Message

A proactive ECMO allocation strategy was employed at the outset of the pandemic. Significant changes were seen in the cohort of patients declined for ECMO over time.

Perspective Statement

Patients who were referred but declined for ECMO in the first wave of the pandemic represent a critically ill cohort with a high mortality rate. A system of tiered selection criteria was created and adopted uniformly across the region in order to select for patients most likely to benefit from ECMO support.

Central Picture

193 patients were evaluated and declined for ECMO using a tiered allocation strategy.

Abstract

Objective: To understand the implications of a tiered ECMO criteria framework and the outcomes of COVID-19 ARDS patients who we were consulted on for ECMO but ultimately declined.

Methods: All patients declined for ECMO support by a large regional health care system between March 2020 and July 2021 were included. Restrictive selection criteria were enacted midway through the study stratifying the cohort into two groups. Primary outcomes included 30-day mortality. Secondary outcomes included reasons for declining ECMO and survival stratified by phase.

Results: 193 COVID-19 ARDS patients were declined for ECMO within the study period out of 260 ECMO consults. At the time of consult, 71.0% (n=137) were mechanically ventilated and 38% (n=74) were proned and chemically paralyzed. 30-day mortality was 66% (n=117) which increased from 53 % to 73% (P=0.010) when restrictive criteria were enacted. Patients with multi-system organ failure, prolonged ventilator time, and advanced age had respectively an 11-fold (OR 10.6, 95% CI 1.7 - 65.2), 4-fold (OR 3.5, 95% CI 1.1 - 12.0), and 4-fold (OR 4.4, 95% CI 1.9-10.2) increase in the odds of mortality**.**

Conclusions: Patients with COVID-19 ARDS declined for ECMO represent a critically ill cohort. We observed an increase in the severity of disease and 30-day mortality in consults in the latter phase of our study period. These findings may reflect our use of tiered selection criteria coupled with ongoing education and communication with referring centers, sparing both patients likely to respond to medical therapy and those who were unsalvageable by ECMO.

Abstract Word Count: 250

Mini-Abstract

Patients who were referred for ECMO but declined in the first wave of the pandemic represent a critically ill cohort with a high mortality rate. Creation of tiered selection criteria in the setting of resource limitations may have aided discernment of patients most likely to benefit from ECMO support from those with high likelihood of response to medical therapy or those who were potentially unsalvageable.

Key Words

COVID-19, ARDS, extracorporeal membrane oxygenation, ECMO criteria, survival

Introduction

Given successes in extracorporeal membrane oxygenation (ECMO) in critically ill patients with acute respiratory distress syndrome (ARDS)[1, 2] during prior respiratory viral outbreaks, its utility in COVID-19 has been widely investigated. Though initial reporting showed variable success[3-6] later ELSO registry data and meta-analyses demonstrated that ECMO is a reasonable intervention in critically ill COVID-19 patients with mortality rates comparable to other indications[7, 8] The overwhelming strain of COVID-19 on healthcare systems in the US during the first year of the pandemic resulted in many patients without access to all available interventions. Much is still to be determined on the best way to stratify and designate patients who will most greatly benefit from ECMO during these times. The outcomes of patients evaluated by a large ECMO center but then ultimately declined using a system of tiered predetermined criteria have not yet been reported. This study evaluates patients with COVID-19 ARDS pneumonia who were consulted for but ultimately declined for ECMO candidacy using a proactive tiered approach.

Methods

All patients who were considered for ECMO at a regional health care system with multi-state catchment area between March 2020 and July 2021 were included. Initial phase criteria took effect until late from March 2020 to November 2020 at which time enhanced selection criteria were utilized for the remainder of the study period. The initial phase was referred to as the "Green" phase and later phase as the "Yellow" phase. All patient data that were provided and available at the time of the initial consult were included. Hospital course and 30-day outcomes were obtained via retrospective review of public records and electronic health record (EHR).

Background of the Hospital System and ECMO Program

The University of Pittsburgh Medical Center is a large regional health system in Western Pennsylvania with a multi-state catchment area. Across its multiple locations it maintains a capacity of 8700 beds. At the onset of the pandemic, as in hospitals all around the country, specific inpatient floors and medical intensive care units were designated for COVID-19 patients. Part of the cardiothoracic ICU at the flagship hospital was transformed into an isolated COVID-19 ECMO unit in which patients were cared for by a dedicated nurse, perfusionist, fellow and attending physician specific to that unit. The capacity for ECMO support varied but averaged between 15-20 patients and was dependent ECMO equipment, hospital capacity, and healthcare personnel staffing, with overall maximum availability of support being around 36. Capacity was never limited during the study period by equipment shortages but by overall hospital bed capacity and ICU staffing shortages. Veno-venous (VV) ECMO cannulation teams comprised of cardiothoracic surgeons, critical care physicians, and perfusionists with the capacity to cannulate remotely if needed. All patient referrals for ECMO within this system were directed to this special team of critical care physicians and surgeons for candidacy consideration. Referrals were initiated by critical care and emergency medicine physicians locally and regionally, with the most remote consult received over 300 miles from our center. Candidacy was initially evaluated by the on-call physician using pre-determined institutional COVID-19 ECMO criteria and subsequently affirmed by a three physician ECMO committee which included two critical care attendings and one cardiothoracic surgeon. To ensure uniformity, the selection criteria and tiered approach were agreed upon by a regional consortium of ECMO

center directors and were distributed to regional Chief Medical Officers (CMOs) prior to the surge of COVID-19 cases in the area.

ECMO Initiation Criteria

Selection criteria were established at the beginning of the pandemic in March 2020. These were developed based upon predetermined standard institutional criteria to objectively identify those with a higher probability of survival (Figure 1). Indications for ECMO support included one of the three criteria used in the EOLIA trial: a PaO2/FiO2 (P/F) ratio of <50mmHg for >3 hours; a P/F ratio <80mmHg for greater than 6 hours; or an arterial blood pH <7.25 with PaCO2 of at least 60mmHg for >6 hours[2]. Exclusion criteria and initial survival predictions were dictated by the RESP score[9] and excluded patients greater than 65 years old, on mechanical ventilation for 10 days or longer, in acute multiorgan failure, and those with significant medical comorbidities (i.e. active cancer, immunocompromised, home oxygen requirement/irreversible lung disease). ECMO support was also declined if the patient met inclusion criteria but had not yet demonstrated failure of medical therapy which including intermittent prone positioning, chemical paralysis, and optimized ventilator settings[10-12]. In these cases, referring physicians were contacted after 24 hours for re-evaluation until a final determination for ECMO candidacy was made. Halfway through the study period the predetermined criteria for "Yellow" Phase were enacted due to capacity restraints on the hospital system as it was overwhelmed by cases. The "Yellow" Phase was triggered by a reduction in capacity for ECMO cases by greater than 50% by the factors previously mentioned. In this phase, age cutoff was lowered to 59 years and mechanical ventilation days were reduced to 7 days or less, which included consideration of both invasive and noninvasive ventilation (i.e. CPAP/BiPAP and high flow nasal cannula (HFNC))

when measuring duration. These criteria were re-distributed and adopted regionally across hospital systems to streamline and standardize access to ECMO for the duration of the pandemic.

Study Inclusion Criteria and Statistical Analysis

All patients between 3-1-20 and 7-31-21 who were referred for consideration of VV ECMO due to COVID-19 induced ARDS were included in this study. SARS-CoV2 positive status was confirmed in all patients via RT-PCR. Patients referred for consideration of veno-arterial (VA) ECMO support were excluded. Study approval was obtained from the hospital Quality Review Committee as Quality Improvement (QI) with Institutional Review Board exemption. All referral calls, which were made both within and outside the hospital system, were facilitated and recorded by a central call system ("Medcall") and subsequently added to a consult database. Patient condition was evaluated over the phone using all provided data available at the time including duration of illness, ventilator settings, arterial blood gas values, basic laboratory values, use of prone positioning, neuromuscular blockade, and medical history. Additional patient data were obtained via retrospective chart review, if available. The 30-day outcomes were obtained by retrospective review of the electronic health record (EHR) and verified by a public record search within the catchment area. Date of death, length of hospital stay (LOS) and discharge data were included if available. Pearson's chi-square tests were used for categorical variables. Wilcoxon and Kruskal Wallis tests were used for continuous variables. Multivariable logistic regression was used to determine predictors of mortality following declining ECMO therapy adjusted for the different phases ("Green" or "Yellow"). Kaplan-Meier estimates with log-rank test were used for time to event analysis.

Results

The period from March 2020 to July 2021 represented the first wave of the COVID-19 pandemic, during which hospitalizations peaked in December 2020 across Allegheny County and Pennsylvania (Figure 2). Within these seventeen months, 260 patients were evaluated and considered for ECMO therapy and ultimately 74.0% (n=193) were declined (Figure 3). Basic demographics and clinical condition at the time of the consult are indicated in Table 1. The cohort was 59% (n=114) male, with a median BMI of 36 (IQR 30 – 43) and age 56 years (IQR 47- 62). Most patients were supported on mechanical ventilation (72%, n=138) with a median PaCO2 of 54 mmHg (IQR 44-65) and P/F ratio of 92 (IQR 71-121). Prone positioning and chemical paralysis were used in 38% (n=74) of patients at the time of consult. Criteria for ECMO consideration became more restrictive approximately 9 months into the pandemic as the volume and severity of patients increased. There were significant differences in the cohort of declined patients between the "Green" and "Yellow" phases. In the latter half of the study, declined patients were notably younger (median age 55, IQR 48-60, p=0.048) and more critically ill, with median PaCO2 of 55 mmHg (p=0.03) and P/F ratio of 86 compared to 108 (p<0.01) in the first phase of consults. The overall mortality of declined patients was 66% (n=117) with an increase in 30-day mortality from 53% (n=31) to 73% (n=86, p = 0.010) across phases. During this study period, 64 patients were cannulated for VV ECMO; 24 in the "Green" phase and 40 during the "Yellow" phase. Overall mortality for patients supported on ECMO was 55%, with 46% mortality in the "Green" phase (n=11), and 60% mortality in the "Yellow" phase (n=24, p=0.27). Median age in cannulated patients was 53.5 in "Green" compared to 49 in "Yellow" (p=0.013).

171 The primary reason for declining the patient for ECMO support was conveyed to the referring
172 physician and documented at the time of the consult. Lack of demonstrated failure of medical
173 therapy, i.e. not yet proned and paralyzed, was the single greatest reason for decline, followed by
174 advanced age, pre-existing comorbid conditions, and prolonged ventilator time (Table 2). When
175 stratified by COVID phase, significantly fewer patients overall were declined due to non-failure
176 of medical therapy as the pandemic progressed (p=0.007). A chi square analysis found that
177 decline reason was associated with survival outcome ($p < 0.001$). Lack of failure of medical
178 therapy (i.e. "too healthy") was associated with better survival ($p < 0.001$), but age and
179 multiorgan failure were associated with poorer survival ($p < 0.05$). There was not an association
180 with survival for other decline reasons (Table 3a). Of the reasons for not offering ECMO, acute
181 multiorgan failure was the strongest predictor of 30-day mortality representing a nearly 11 fold
182 increase in risk (Table 3b, OR 10.6, 95% CI 1.71 – 65.2, $p = 0.011$), followed by age (OR 4.43,
183 95% CI 1.93 – 10.2, $p < 0.001$), ventilator time (OR 3.54, 95% CI 1.05 – 12.0, $p = 0.04$), and
184 pre-existing comorbidities (OR 3.14, 95% CI 1.09 – 9.09, $p = 0.03$).
185
186 Significant differences in patients declined for ECMO were noted between those who survived
187 and those who died within 30-days post-consult (Table 4). Patients that died were frequently
188 older (median age 58 versus 54 years, p=0.002) and more critically ill at the time of consult, with
189 greater median PaCO2 of 56mmHg (IQR 48 – 67) compared to 50mmHg (IQR 41-58, p=0.028),
190 higher FiO2 of 100% compared to 95% in survivors (p=0.029) and had a significantly lower P/F
191 ratio of 86 (IQR 65-112) compared to 106 (IQR 79-146, p=0.005). Survival analysis found a
192 trend towards difference in survival time. Patients in the latter "Yellow" phase had shorter

survival durations (Table 5, Figure 4; median 12 days, 95% CI: 9-18 days) relative to patients in the "Green" phase (median 15 days, 95% CI: 10 – Inf. days, χ^2 (1) = 3.8, p = 0.053).

Discharge data were available for 53 (27.4%) of the referrals who represented 89.8% of all survivors (Table 6). In this group of patients declined for ECMO, the median inpatient length of stay was 31.0 days (IQR: 19- 42). Discharge was either to home (43%, n=23), inpatient rehabilitation (28%, n=15), or LTAC (28%, n=15). Median duration on mechanical ventilation was 14 days (IQR 10-20) until either extubation (54%, n=26) occurred or tracheostomy (46%, n=22) was performed. Patients discharged to home had shorter overall LOS (median 19 days), shorter ventilator duration (median 10 days) and had higher rates of extubation (84%) relative to patients discharged to IPR or LTAC ($p<0.05$).

Discussion

In this study, we describe the use of a tiered system of selection criteria for ECMO that was universally adopted across health systems within our region. This approach was designed to flex with changes in capacity and available resources in order to provide consistent access for those most likely to benefit from support. Patients declined for ECMO candidacy using these criteria were retrospectively evaluated, providing insight into both the impacts of this framework and the natural course of the COVID-19 pandemic.

The initial wave of COVID cases abroad and in the eastern US prompted discussions within our team to create a comprehensive strategy for ECMO utilization. It was critical to pre-emptively develop a framework for ECMO initiation criteria using the best available evidence at the time

which pointed to the relative success of this intervention in COVID-19 patients. Concurrently, the finite resources of the hospital system and the community at large were considered. Prior institutional experience in dealing with the H1N1 pandemic in 2009 informed the knowledge that maximum hospital capacity would be accompanied by a surge in ECMO consultations. Our first step was to adjust our standard ECMO criteria in the context of the resources of our hospital and ECMO program to identify trigger points at which ECMO candidacy should be restricted. There are notable ethical challenges to consider when allocating high-cost resources in limited availability situations, such as whether to prioritize the sickest versus those who "come first," or those with the highest chance of survival[13]. Our institutional priorities were to maximize our ability to offer ECMO to patients with a reasonable likelihood of survival while minimizing the chance of having to decline a candidate due to lack of capacity. Given the substantial physical resources, personnel and coordination required to maintain an ECMO program[14] this required careful institutional inventory and preparedness assessment. With these goals and information, we created our framework of "Green," "Yellow," and "Red" criteria which was discussed with regional stakeholders across healthcare systems and proactively distributed to all hospitals in our catchment area. By establishing a single framework adopted among multiple medical centers, we were able to maximize our collective ability to provide equitable patient care, eliminating disparities in geographic area or insurance coverage.

A comparison of declined patients from the "Green" and "Yellow" phases reveals two types of consults. On one hand were "healthier" patients with better oxygenation and ventilation (lower median PaCO2, higher median P/F ratio), including some who were not yet intubated. Others met inclusion criteria but were initially declined because proven interventions such as proning

and chemical paralysis had not yet been performed. These patients had a significant chance of improving with further medical management. The other group of patients were older, had been intubated for several days, or were developing multiorgan failure, and represented a cohort so critically ill that ECMO support was unlikely to alter their trajectory.[15] Initial survival comparisons between patients declined for ECMO and those who were cannulated for ECMO during this seventeen month period reveal that mortality increased in both groups over time. Overall patients were getting sicker despite our increased understanding of how to manage the disease. A non-significant increase in mortality in the cannulated patients during the "Yellow" phase supports the transition to stricter selection criteria as laid out in our framework. Our overall survival with ECMO is consistent with national mortality rates published by ELSO during the same period.[7]

Additional differences in the phases of declined patients support the success in our data dissemination strategy. The lower median age of patients declined in the "Yellow" phase is an expected change. As the age requirement for ECMO consideration lowered, so did the group of patients that were no longer eligible. The data also reveal that fewer elderly patients were being referred for ECMO in this stage, which supports the notion that the referring centers had become increasingly familiar with our criteria. Fewer patients were declined for ECMO because of being "too healthy" in the latter half of the study period, as physicians in outside hospitals likely (1) became increasingly familiar with our ECMO candidacy criteria, (2) employed evidence-based strategies as they became available, and (3) developed more experience caring for these critically ill patients. Furthermore, consulted physicians at the ECMO center had repeated opportunities to provide education and counseling to the physicians on the referral call or follow-up call with

regards to best practices for this cohort. Rather than confine the consult to one or two conversations, consulting physicians were encouraged to call back if the patient condition did not improve with strategies discussed, and our team was able to provide additional support at all times. Out of the 131 patients declined in the "Yellow" phase, we found thirty potential candidates for ECMO under the "Green" phase criteria had the more liberalized ranges for patient age and ventilator time been used. This does not account for the possibility of uncovering multiple exclusion criteria had the evaluation progressed. Mortality in this group of patients was 80% (n=24).

Varying selection and management strategies were employed at ECMO centers around the country at the beginning of the pandemic. In establishing their criteria, each center was at risk of missing an opportunity to offer ECMO to patients that could benefit. Overly strict criteria that restricts access to ECMO to only the young and otherwise healthy may miss patients who would survive with the support of ECMO, while overly liberal criteria may result in the system becoming overwhelmed with patients who won't survive. Institutions that utilized more liberalized criteria offering ECMO to those with advanced age and single organ dysfunction had unsurprisingly higher mortality rates[16] than those with stricter criteria; in contrast, initial reporting out of NYU demonstrated markedly higher survival rates in patients who were younger (median age 40) and with a higher median P/F ratio (84) at time of cannulation.[17] Gannon et al utilized similar criteria to our institution during the pandemic though were limited by capacity and ultimately able to cannulate and support only 40% of patients that met their criteria.[18] While in some respects this can be interpreted favorably, as every available ECMO bed was utilized, it also highlights the challenge that all ECMO centers faced during the pandemic: that the needs of

our hospital systems far outpaced our capacity. At our center, the criteria became progressively stricter, even reaching "red phase" with an age cutoff of 50 years old at a later surge in COVID-19 cases not covered in this analysis. Despite the large number of patients who were ultimately declined for ECMO during this study period, the application of this selection criteria had positive impacts beyond creating a uniform regional response. Referring physicians received unequivocal answers that could be put into practice immediately, whether that was critical care guidance or a declined ECMO case which could facilitate end of life conversations. With clear guidelines that were adhered to throughout the region, physicians on the ECMO team were similarly unburdened of feeling solely responsible for a decision during this time of great emotional strain.

There were many potential areas for improvement in the implementation of our ECMO referral criteria. First, there was some lack of standardization in what was considered positive pressure ventilation. While it is known that ARDS patients with shorter duration between intubation and cannulation have improved survival,[9] the effects on survival of non-invasive positive pressure ventilation (BiPAP, HHFNC) are not well defined.[19] Our decision to include non-invasive ventilation when counting days on respiratory support was driven by our observations that intubation was being delayed until later in the disease process when the fibrotic stage of ARDS was setting in. Secondly, we did not have a system in place to check on the consults in real time. Though the ECMO team made follow-up calls for all patients that were being considered for management suggestions, most of the medical management was guided by the physicians at referring hospitals. In addition, while lung transplant is a potential option for patients with irreversible lung injury due to COVID-19,[20] our criteria was not constructed for the cohort of patients requesting ECMO as a bridge to transplantation. In addition, since we were unable to

directly review the outside hospital medical records for all patients, our knowledge of the extent of medical management was frequently limited to verbal confirmation of prone positioning, positive pressure ventilation, and chemical paralysis. We do not have information on COVID-19 specific medical management with steroids or antibody therapy that may have benefitted certain groups of patients seeking ECMO support. We were also limited in our ability to identify and track the COVID-19 variants in this cohort, which may have additionally impacted survival. As the local physicians became more familiar with our ECMO candidacy criteria, it is possible that we received fewer referrals for patients who would be turned down, which may have biased our results. Finally, this is a retrospective study with all of the inherent limitations in its design.

ECMO has proved to be a valuable tool in supporting patients with ARDS caused by COVID-19. We present a proactive allocation and triage strategy that was used successfully to balance the needs of acutely ill patients with COVID-19 **ARDS** against the finite resources of our hospital system during the beginning of the pandemic. Using this framework, we identified patients who were not appropriate for ECMO support either due high risk of mortality or high likelihood of improvement without ECLS. Further research is needed to determine optimal criteria to provide maximal survival benefit for this disease. Particularly in times of strain on the health care system, high resource interventions need to be allocated thoughtfully with mechanisms in place to track outcomes and provide feedback for improvement.

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Table 1. Patient Characteristics

Characteristic	N	Overall, N = 193[1]	COVID Green Phase, N = 62	COVID Yellow Phase, N = 131	p-value[2]
Age, Median (IQR)	193	56 (47 – 62)	58 (46 – 68)	55 (48 – 60)	0.048
Sex, n (%)	193				0.078
Female		79 (41)	31 (50)	48 (37)	
Male		114 (59)	31 (50)	83 (63)	
Body Mass Index (kg/m2), Median (IQR)	133	36 (30 – 43)	36 (30 – 43)	36 (30 – 43)	0.85
PaO2, Median (IQR)	144	77 (65 – 100)	79 (70 – 108)	75 (64 – 94)	0.087
PCO2, Median (IQR)	135	54 (44 – 65)	52 (41 – 57)	55 (47 – 68)	0.030
FiO2, Median (IQR)	159	1.00 (0.80 – 1.00)	0.90 (0.70 – 1.00)	1.00 (0.80 – 1.00)	0.015
PEEP, Median (IQR)	147	14.0 (12.0 – 16.0)	13.2 (10.0 – 15.0)	14.0 (12.0 – 16.0)	0.084
P/F Ratio, Median (IQR)	138	92 (71 – 121)	108 (86 – 156)	86 (66 – 106)	<0.001
Proned & Paralyzed at Consult, n (%)	193	74 (38)	27 (44)	47 (36)	0.31
30 Day Mortality, n (%)	176	117 (66)	31 (53)	86 (73)	0.010

[1]Median (IQR); n (%)

[2]Wilcoxon rank sum test; Pearson's Chi-squared test

Table 2. Reason for ECMO Decline

Characteristic	N	Overall, N = 193[1]	COVID Green Phase, N = 62	COVID Yellow Phase, N = 131	p-value[2]
Reason for Decline, n (%)	193				
Lack of Failure of Medical Therapy		70 (36)	31 (50)	39 (30)	0.0069
Pre-existing Comorbidity		25 (13)	6 (9.7)	19 (15)	0.37
Multiorgan Failure		14 (7.3)	3 (4.8)	11 (8.4)	0.37
Age		54 (28)	18 (29)	36 (27)	0.84
Body Mass Index		6 (3.1)	0 (0)	6 (4.6)	0.09
Ventilator Time		19 (9.8)	4 (6.5)	15 (11)	0.27
Duration of Illness		3 (1.6)	0 (0)	3 (2.3)	0.23
Other		2 (1.0)	0 (0)	2 (1.5)	0.32

[1]n (%)

[2]z-test of column proportions

Table 3a. Differences in Survival Across Decline Codes.

Characteristic	N	Overall, N = 176[1]	Alive, N = 59	Deceased, N = 117	p-value[2]
Decline Code, n (%)	176				<0.001
Lack of Failure of Medical Therapy		63 (36)	36 (61)	27 (23)**	
Pre-existing Comorbidity		23 (13)	6 (10)	17 (15)	
Multiorgan Failure		14 (8.0)	1 (1.7)	13 (11)*	
Age		52 (30)	11 (19)	41 (35)*	
Body Mass Index		4 (2.3)	1 (1.7)	3 (2.6)	
Ventilator Time		17 (9.7)	4 (6.8)	13 (11)	
Duration of Illness		3 (1.7)	0 (0)	3 (2.6)	
Other		0 (0)	0 (0)	0 (0)	

[1]n (%).

[2]Fisher's exact test

*p < 0.05, **p < 0.001 post hoc.

Table 3b. Predictors of 30-day Mortality.

Characteristic	N	OR (95% CI)[1]	p-value
Decline Reason	176		
Lack of Failure of Medical Therapy		ref.	
Duration of Illness		7.22 (0.22 to 233)	0.26
Pre-existing Comorbidity		3.14 (1.09 to 9.09)	0.034
Multiorgan Failure		10.6 (1.71 to 65.2)	0.011
Age		4.43 (1.93 to 10.2)	<0.001
Body Mass Index		2.41 (0.26 to 22.2)	0.44
Ventilator Duration		3.54 (1.05 to 12.0)	0.042
Era	176		
Early COVID Era		—	
Refined COVID Era		1.71 (0.84 to 3.48)	0.14

[1]OR = Odds Ratio, CI = Confidence Interval

Table 4. Patient Characteristics Across Survival Status.

Characteristic	N	Overall, N = 176[1]	Alive, N = 59	Deceased, N = 117	p-value[2]
Age, Median (IQR)	176	56 (48 – 62)	54 (42 – 59)	58 (49 – 64)	0.002
Sex, n (%)	176				0.17
Female		71 (40)	28 (47)	43 (37)	
Male		105 (60)	31 (53)	74 (63)	
Body Mass Index (kg/m2), Median (IQR)	125	36 (30 – 43)	38 (31 – 43)	34 (28 – 41)	0.11
PaO2, Median (IQR)	137	79 (65 – 102)	80 (68 – 108)	76 (65 – 95)	0.14
PCO2, Median (IQR)	128	54 (45 – 65)	50 (41 – 58)	56 (48 – 67)	0.028
FiO2, Median (IQR)	149	1.00 (0.80 – 1.00)	0.95 (0.70 – 1.00)	1.00 (0.80 – 1.00)	0.029
PEEP, Median (IQR)	139	14.0 (10.0 – 15.0)	12.0 (10.0 – 15.0)	14.0 (10.5 – 15.8)	0.29
P/F Ratio, Median (IQR)	131	91 (69 – 122)	106 (79 – 146)	86 (65 – 112)	0.005
Prone & Paralyzed at Consult, n (%)	176	68 (39)	24 (41)	44 (38)	0.69

[1]Median (IQR); n (%)

[2]Wilcoxon rank sum test; Pearson's Chi-squared test

Table 5. Kaplan-Meier Survival Estimates - Post-Consult

Characteristic	7 Days	14 Days	21 Days	28 Days	p-value
COVID Era					0.053
"Green" Early COVID Era	70% (59% to 83%)	52% (40% to 67%)	47% (35% to 63%)	44% (32% to 60%)	
"Yellow" Refined COVID Era	65% (56% to 75%)	41% (32% to 52%)	33% (25% to 44%)	27% (19% to 38%)	

Table 6. Discharge Data

Characteristic	N	Overall, N = 53[1]	Home, N = 23	IPR, N = 15	LTAC/Select, N = 15	p-value[2]
Length of Stay, Median (IQR)	50	31 (19 – 42)	19 (15 – 32)[a]	38 (28 – 45)[b]	39 (31 – 42)[b]	0.003
Prone and Paralyzed at Consult, n (%)	53	24 (45)	9 (39)	8 (53)	7 (47)	0.69
Age, Median (IQR)	53	54 (41 – 58)	45 (34 – 56)	55 (49 – 57)	55 (48 – 60)	0.21
Sex, n (%)	53					0.054
Female		25 (47)	15 (65)	6 (40)	4 (27)	
Male		28 (53)	8 (35)	9 (60)	11 (73)	
P/F Ratio, Median (IQR)	43	103 (75 – 153)	90 (73 – 123)	113 (79 – 162)	119 (88 – 134)	0.42
Duration to Extubation/Tracheostomy, Median (IQR)	47	14 (10 – 20)	10 (8 – 13)[a]	16 (14 – 20)[b]	19 (13 – 24)[b]	0.003
Ventilation, n (%)	48					<0.001
Extubation		26 (54)	16 (84)*	8 (53)	2 (14)*	
Tracheostomy		22 (46)	3 (16)*	7 (47)	12 (86)*	

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Figure 1.

ECMO selection criteria adjusted for systemwide capacity. Distributed as part of detailed ECMO criteria and critical care guidelines to hospital system and regional stakeholders.

Figure 2.

Study period spanning the first seventeen months of the pandemic, beginning with Green Phase criteria and transitioning to more restrictive Yellow Phase criteria just before the first peak of cases in Allegheny County, Pennsylvania and across the state. *Adapted from Allegheny County Health Department (alleghenycounty.us)*

Figure 3.

193 patients were evaluated and declined for ECMO out of 260 COVID-19 ECMO consults using a tiered allocation strategy.

Figure 4.

Kaplan-Meier Survival Stratified by Consult Phase.

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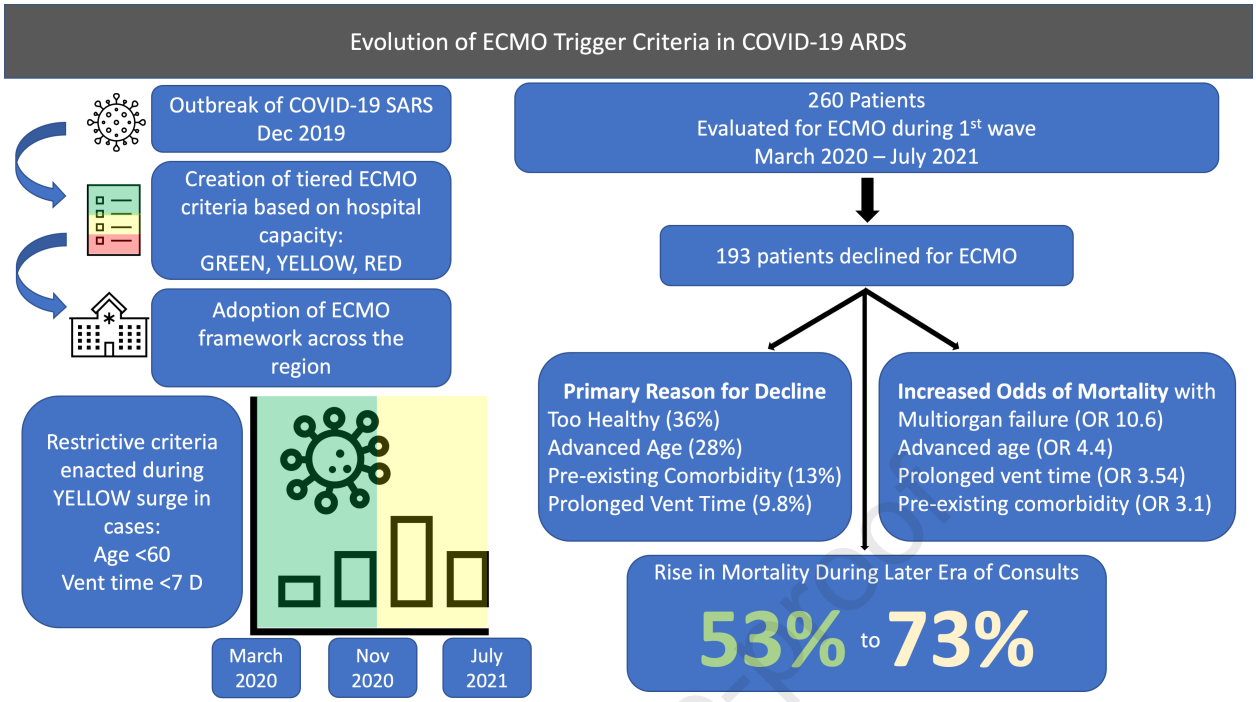
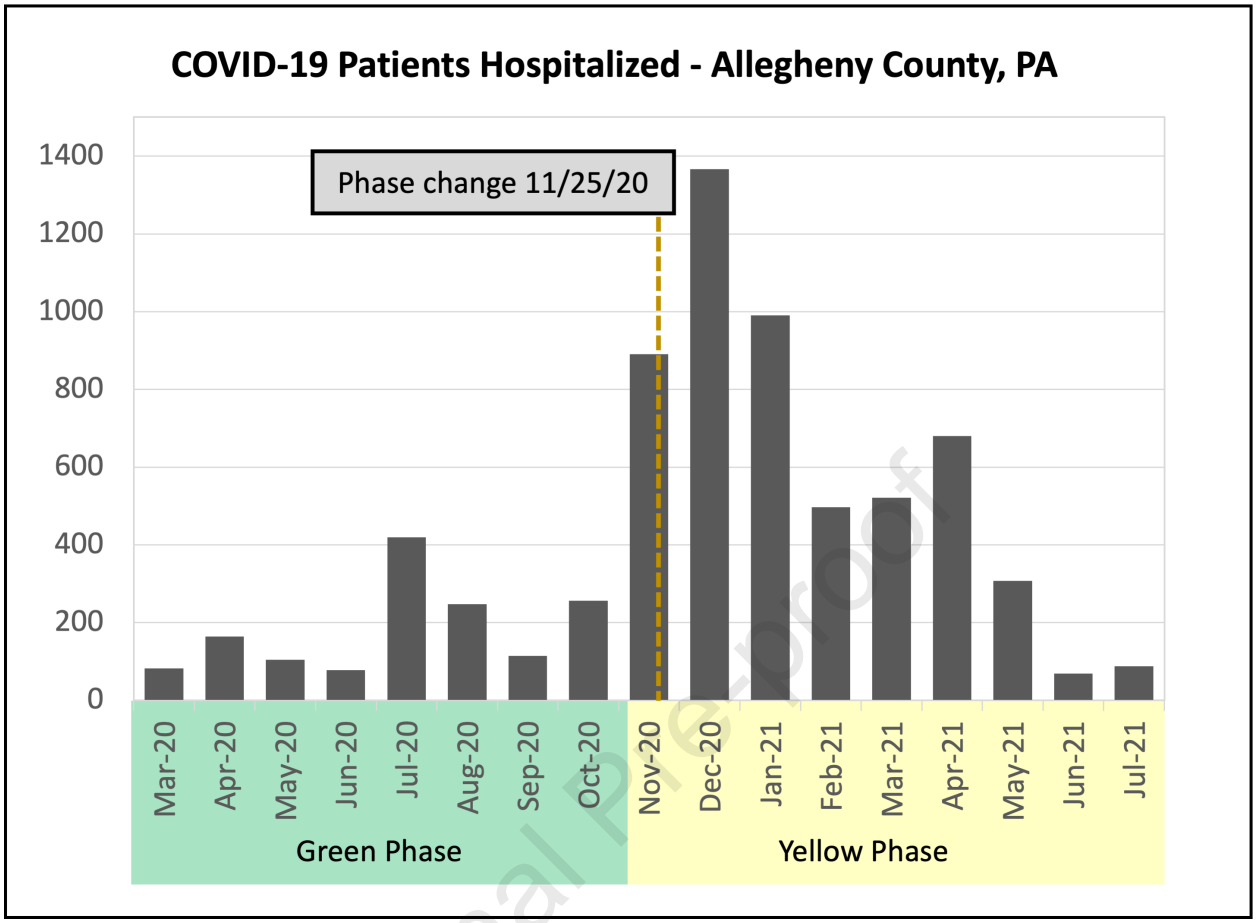
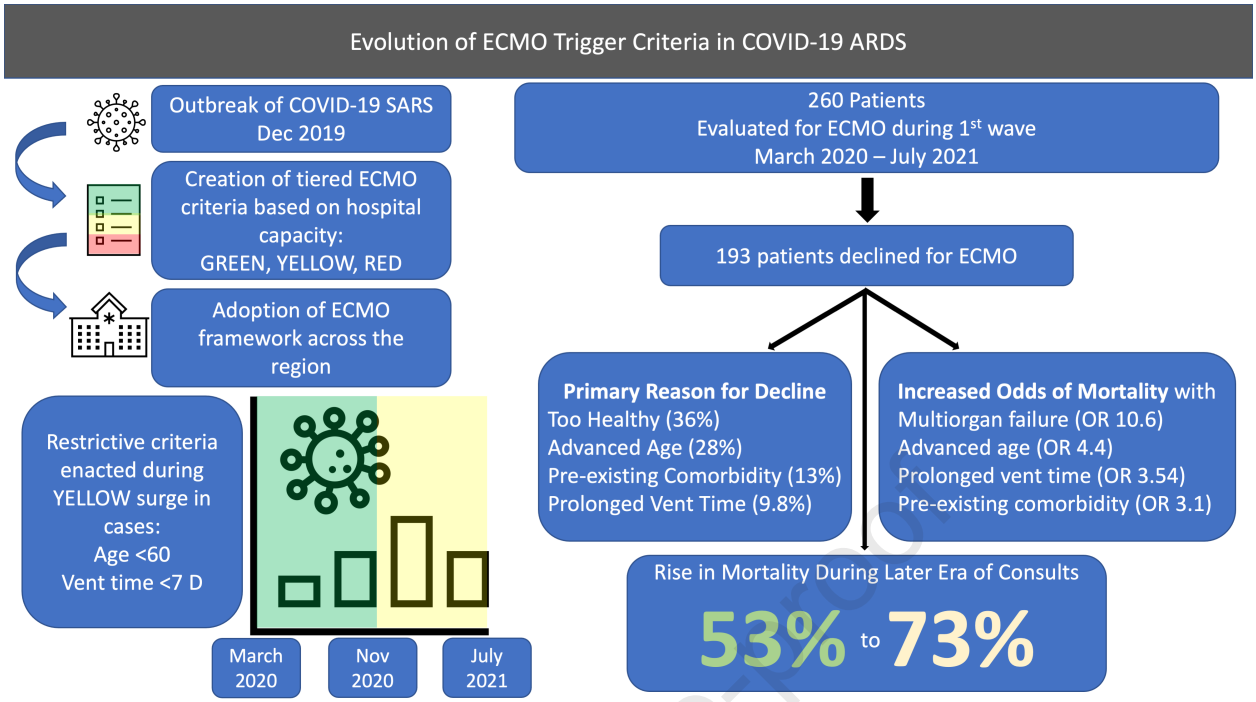
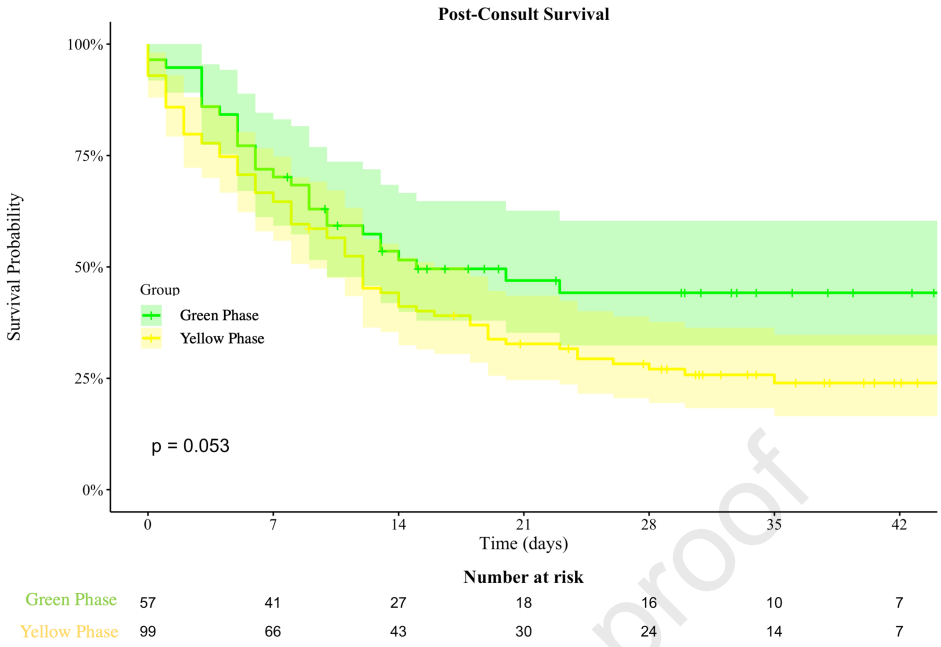


- Standard Operating Capacity (>10 ECMO Machines available)
  - UPMC standard selection criteria and standard exclusion criteria
    - Age <65 y/o
    - Mechanical ventilation <10 days
  - RESP Predicted Survival >57%
- System at >50% capacity
  - Enhanced selection criteria and enhanced exclusion criteria
    - Age <60 y/o
    - Mechanical Ventilation <7 days
    - No pre-ECMO cardiac arrest
    - PIP <42 cmH_2O
  - RESP Predicted Survival >76%
- System at >75% capacity
  - Stringent selection criteria and enhanced exclusion criteria
    - Age <50 y/o
    - Mechanical ventilation <5 day
    - No pre-ECMO cardiac arrest
    - PIP <42 cmH_2O
  - RESP Predicted Survival >92%







Number at risk

Green Phase	57	41	27	18	16	10	7
Yellow Phase	99	66	43	30	24	14	7


Journal Pre-proof

AATS 2022 Annual Meeting

Evolution of ECMO Trigger Criteria in COVID-19 ARDS

Presenter: Dr. Rachel Deitz

Invited Discussant: Dr. Nathalie Roy

Dr. Nathalie Roy (Boston, MA):

I would like to thank the AATS for the opportunity to discuss this manuscript and also thank the authors for providing me a copy of the manuscript in advance of the meeting. You report outcomes of patients who were referred for, but not supported on ECMO, based on your tiered triage system established early in the COVID pandemic. The system was established proactively to ensure equitable resource utilization and optimal outcomes, and that's what I will focus on with my questions.

First, I want to congratulate you on this effort. Early in the pandemic, the editorial board of the New England Journal of Medicine published a “fair allocation of scarce medical resource” paper, and while the benefit of ECMO was unclear at that time, it became obvious from the Paris group and other authors, in propensity match studies, that there was a significant survival advantage with this ECMO technology. Your presentation reflects the natural history of severe COVID ARDS disease. In that context, I first want to reflect on the severe toll of the pandemic, which has taken the lives of 6.3 million documented humans.

My questions are the following: You described in your manuscript patients that were “too healthy” or did not have optimal medical therapy – what was the survival of this specific cohort? Did you look at it? And how many patients were then later clinically reassessed by your group for a second consultation?

Dr. Rachel Deitz (Pittsburgh, PA):

I'll answer the last question first. The consultation was an active process in which we were constantly discussing with the critical care physicians at the outside hospitals. We would give them suggestions such as ventilatory management, use of proning and paralysis, and we made sure that we returned phone calls or called them back within a 12-hour time period to ensure that those strategies were being employed. And we also encouraged continued communication with us. Although, it's possible that a few of those patients may have gotten lost to follow-up, just because the consults were coming in so frequently. To answer your first question, I don't have the exact value for patients that were "too healthy," but in a different calculation, we did find it to be a protective benefit against mortality.

Dr. Roy:

Thank you. Did you consider propensity matching the patients who are refused as your phase evolved from green to yellow, and now to red – further on in the pandemic, in your cohort of non-supported patients?

Dr. Deitz:

I think our statistical analysis was a little limited because we gathered all the information that we had available to us from these referring hospitals, in a series of small snapshots of how the patients were doing over time. And because a lot of these patients were out of network, we weren't able to compare a lot of their variables.

Dr. Roy:

Thank you. In your manuscript, you mentioned that this data has helped to counsel families for patients who are not eligible, In the future and with the knowledge of this data, what have you done—I guess my question is, what have you learned and what would you do if there was a dramatic change in the course of this pandemic or if there was a new pandemic?

Dr. Deitz:

Well, it's a good question. Our preliminary data, when we talked about the overall mortality rates in the green phase and the yellow phase—while we were initiating those conversations with the critical care physicians at outside hospitals, we were able to sort of clearly tell them, "Well, this is our criteria and from what we've seen, you may expect X mortality rate for this patient." And I think that helped those physicians in initiating those conversations with families in making important end-of-life decisions. And I think it's important, going forward, to continue to reevaluate this data. Of course, we didn't look at our delta wave red phase criteria yet, so that would be an area for further study.

Dr. Scott Silvestry (Orlando, FL):

I enjoyed your paper. I think it's a very thoughtful, contemplative look at what we did and what we might be able to do in the future. It's very difficult because if you look at your data that suggests that young patients have the best chance of survival if they're declined, but they also have the best chance on ECMO—in the previous talk with Dr. Jeffrey Jacobs' group, they noted that younger age is the primary driver of survival. So when you talk about equity, it would be interesting to see if you can model what survival looks like for the declined patient and, paradoxically, the patient with the best survival and the best use of resources. One model for scarcity allocation requires that they get the VV-ECMO, yet they have the best chance of

surviving outside the lifeboat, so to speak. And so to follow up on the other question, what criteria should we use to select patients in a scare resource (whether we're red or black)—and what criteria *shouldn't* we use? Because 57% survival for the young patients declined is actually better than the ECMO survival in many series depending on it. And so I have to rethink—I mean, we took care of almost 200 COVID ECMO patients at our institution, and I have to think about what we did and what we should do. And tell me what we should do.

Dr. Deitz:

Thank you for your question. That of course necessitates a more in-depth conversation, but I agree—it's challenging to figure out where the sweet spot is between whether patients are going to have a good chance of survival outside of ECMO or whether we're doing them justice by putting those patients on.

Dr. Silvestry:

I was involved in our health system's model for allocation, and one of the non-physician stakeholders who was part of the health system is a businessman, and he makes the glue that holds together all the boxes in the United States. So he's a very successful businessman, and he said it should be first come, first served. And this perspective is just as valid when applied to the allocation of medical resources.

Dr. Deitz:

Indeed.

Dr. Pablo Sanchez (Pittsburgh, PA):

I'm one of the senior authors, and I just want to help clarify a few things. The UPMC system is comprised of 34 hospitals. Before all this, most patients would get transferred to UPMC Presbyterian, where our ECMO center is—either to the MICU if you had severe ARDS, or to a CT surgery ICU for ECMO. So one of the things that changed is that we had to stop that. We could not transfer every single ARDS patient to UPMC Presbyterian anymore, it was impossible. So one of the gains of all this was that the severity of illness that our branching hospitals were able to handle increased, not only through the education of what were the criteria, but also what were the best practices of ARDS. So in a way, it served to raise the bar in our associated hospitals. That's one of the things that improved.

What proportion of healthy patients were put on ECMO eventually? I'll say it was around 25%. That's a very good estimate. Our ECMO survival was around 50%. It was not really off of what we've seen before. The one thing that I think is worth discussing is that, at any point, we'll have

anywhere between 14 and 18 patients on ECMO, but we never reached that level. And I think we never reached it because of all the way we tried to stratify our selection process.

Dr. Rakesh C. Arora (Cleveland, OH):

I think it was just answered by Dr. Sanchez. But just so I understand what the capacity criteria was, was it based on the number of ECMO circuits, capacity in the ICU, hospital capacity of overall COVID burden? Or do all the above factor into that?

Dr. Deitz:

Thank you for the question. Our availability was never limited by ECMO circuits. It was limited by overall hospital capacity and specifically nursing staff in the ICU which, as we all know, was a really big challenge during this time.

Dr. Arora:

Thank you. Of your three criteria, the one I found curious was for the red one. While in addition to the age criteria, the predicted survival was 92%. I'm not sure I put many of those patients on ECMO. Do you have a rough idea of how you came to that criteria and how many people you would have anticipated that would have met that?

Dr. Deitz:

Sorry, can you repeat that again?

Dr. Arora:

So if I understand your slide correctly with the three different colored categories, the estimated survival for someone in the red category level of crisis, you'd have to have a predicted survival of 92% to benefit from ECMO. That’s a really restrictive group and maybe not if you needed ECMO. Could you comment on that particular selection criteria choice?

Dr. Deitz:

Sure. That estimate of survival is certainly not based specifically on COVID-19 patients that would have been put on ECMO.

Dr. Sanchez:

To help clarify: When we established these criteria, we were borrowing data that was published from early COVID experiences and ECMO outcomes that were ARDS-related. We believed that based on those criteria, the expected survival of that population should be 92%, but maybe it's not. So that was when we were trying to justify why we were only allocating ECMO for that really tight group of red. So that wasn't the real survival. That was our expectation of what the survival should look like in that group.

Moderator:

Great. Thank you very much.

Dr. Deitz:

Thank you.