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Defining the Late Implementation of Extracorporeal Membrane Oxygenation (ECMO) by Identifying Increased Mortality Risk Using Specific Physiologic Cut-Points in Neonatal and Pediatric Respiratory Patients

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Abstract: There is no reliable clinical indicator showing how long extracorporeal membrane oxygenation (ECMO) implementation can be delayed before the risk of death becomes unacceptably high in neonatal and pediatric respiratory patients. However, the late use of ECMO may be defined by the elevation of specific physiologic markers separate from pulmonary function and hemodynamic assessments that indicate when the optimal time for implementation of ECMO has past, resulting in a higher than normal mortality, possibly due to reperfusion injury. Neonatal patients were reviewed retrospectively to determine if later implementation of ECMO correlated to increased mortality. Neonatal and pediatric respiratory patients placed on ECMO were reviewed retrospectively to determine if the first adjusted anion gap (AGc), the first venoarterial CO_2 gradient (p[v-a]CO_2), or the first Viability Index (AGc + p[v-a]CO_2 = INDEX) on ECMO could be used to identify a cut-point for increased mortality. Expired neonates (n = 31) were placed on ECMO an average of 2 days later than neonatal survivors (n = 163). The review of 210 respiratory neonatal and pediatric ECMO patients with an overall survival of 82% showed that all three markers were elevated in the expired patients (n = 38, p < .05). Cut-points were an AGc ≥ 23 mEq/L, the p[v-a]CO_2 ≥ 16 mmHg, and the INDEX ≥ 28. These values correlated with a significantly higher risk of mortality (p < .05); survival to discharge being 43% or less. Patients under the cut-points had survival rates of 84% or higher. Starting ECMO too late may cause reperfusion injury that reduces survival. This study describes specific physiologic markers taken soon after ECMO initiation that correlate with mortality. These markers, if assessed earlier, may allow for a more timely ECMO implementation and higher survival.
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Extracorporeal membrane oxygenation (ECMO) is an invasive and potentially hazardous form of therapy proven to save lives, but unnecessarily early implementation of ECMO may expose the patient to dangerous and even fatal complications like those enumerated by the Extracorporeal Life Support Organization (ELSO) registry (1). Conversely, the late implementation of ECMO is also of great concern due to the potential for fatal outcome from advanced morbidity (2). To prevent this, ECMO practitioners rely on an adopted set of formalized indicators, including pulmonary, hemodynamic, and physiologic assessments, as well as their own experience, to determine when to initiate this form of therapy to prevent early or late implementation (3–6).

Over the last 20 years, neonatal ECMO survival has declined in the most common diagnostic groups (Figure 1). The suggestion is that newer therapies are keeping less ill neonates off ECMO, with the remaining infants being sicker and less viable on ECMO (7). However, an alternate explanation may be that the failure of newer therapies might result in the loss of valuable time, with the neonates being placed on ECMO too late for optimal survival. If the late use of ECMO can be defined by the elevation of specific physiologic markers separate from pulmonary function or hemodynamic assessments then the optimal time for implementation of ECMO could be determined. This might reduce the mortality in both neonates and older patients.

Despite examination of many pulmonary and cardiac risk factors, there has been no reliable indicator that provides a critical cut-point that can be used to change

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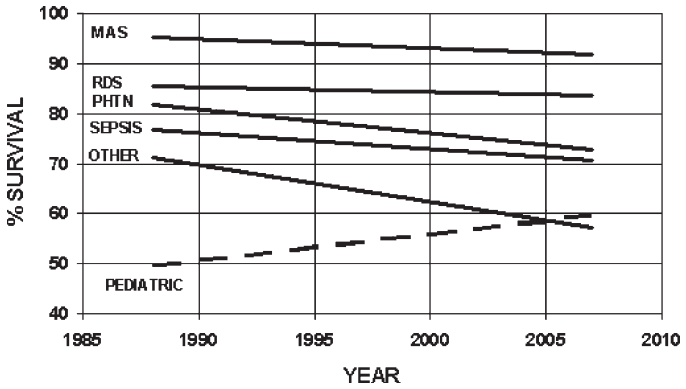

Figure 1. Neonatal and pediatric respiratory ECMO patients: survival trend over time. MAS, meconium aspiration; RDS, respiratory distress syndrome; PHTN, pulmonary hypertension; SEPSIS, infection related respiratory failure; OTHER, less common causes of neonatal respiratory failure; PEDIATRIC, all pediatric diagnoses. Analysis of information from ECLS Registry Report, January 2009, International Summary of the Extracorporeal Life Support Organization, 1327 Jones Drive, Suite 101, Ann Arbor, MI 48105; years 1988 through 2007.

management strategy and improve results (8–10). The cut-point is defined as a physiologic tipping point at which survival greatly declines beyond the normally expected level. Figure 1 illustrates the survival trends over time based upon the ELSO registry and establishes a normally expected level of survival within a large population (1). The population reviewed in this article had 172 survivors out of 210 patients, or 82% survival (Table 1). Placing a patient on ECMO after the cut-point is exceeded may define when it is too late for ECMO if those patients have a lower than expected level of survival.

By inference, a patient placed on ECMO too late will not survive. Knowing not only when it is too late for ECMO, but why it is too late for ECMO, may make it possible to implement a successful strategy different from conventional ECMO for those late patients.

The average anion gap (AG in mEq/L) and the average venoarterial CO_2 gradient (p[v-a]CO_2 in mmHg) of patients on ECMO correlate directly with survival; elevated values are associated with poor survival (11). Adjusting the AG for low serum albumin and elevated blood urea nitrogen (BUN) values improves its predictive value. The average adjusted anion gap (AGc) and the average p[v-a]CO_2 are each independently capable of a limited prediction for survival in many ECMO patients who have no lethal anatomic defects (12).

However, the combination of these two markers into a final average Viability Index (INDEX) has been demonstrated to provide the best correlative prediction for survival (12). The final average INDEX value is calculated by including values at the beginning of ECMO through values at the end of ECMO (Figure 2). Since the final average INDEX value can only be calculated once the patient is removed from ECMO, its predictive value is limited.

The authors hypothesize that if the first INDEX value on ECMO is elevated beyond a certain cut-point, then the survival of respiratory ECMO patients will be greatly diminished. This review will analyze the ability of the first INDEX after the implementation of ECMO to identify these high risk patients. The supposition is that an INDEX monitored before ECMO may prevent the late implementation of ECMO.

MATERIALS AND METHODS

Institutional Review Board Authorization

This review is authorized by Children's Mercy Hospitals and Clinics of Kansas City, MO, Pediatric Institutional Review Board protocol # 03–06–067X entitled "A Descriptive, Retrospective Review of All Patients with Congenital Heart Disease Presenting to the Children's Mercy Hospital from 1980 to Present." It was approved in June 2003, reviewed and renewed annually and by a February 2005 amendment to specifically include "A Descriptive, Retrospective Review of Patients Undergoing Extracorporeal Membrane Oxygenation (ECMO) from 1987 to the Present". This amendment is also reviewed and renewed annually.

Data Collection

ECMO patient data was collected from November 1989 through December 2008. The very first Viability Index values on ECMO of 210 respiratory patients were retrospectively examined to determine the correlation to survival. Survival was defined as survival to discharge. All patients were ELSO classified as respiratory ECMO patients (1).

The first AGc was drawn within a few hours after the initiation of ECMO. Blood was drawn from the venous line of the ECMO pump. Serum electrolytes were used in all calculations. The unadjusted anion gap was calculated using the following formula (13):

$$\text{Unadjusted anion gap} = \text{serum sodium} - (\text{serum chloride} + \text{serum bicarbonate})$$

Albumin and BUN measurements were sampled concurrently and used to calculate the AGc using this formula (12,14):

$$\text{Adjusted anion gap} = \text{Unadjusted anion gap} + ([4 - \text{albumin}] \times 2.5) - ([\text{BUN} - 15] \div 7)$$

The first p[v-a] CO_2 was drawn at the same time as the AGc. The p[v-a] CO_2 was calculated using the post-ductal arterial blood gas ($paCO_2$) and a venous blood gas ($pvCO_2$) from the venous return line to the ECMO pump. In the few patients who were on venovenous ECMO, the $pvCO_2$ was drawn from a cephalic vein drainage cannula to avoid mixing with recirculated blood from the oxygenator. The following formula was used to calculate the gradient (15):

Table 1. Respiratory ECMO patients: Diagnosis, age ECMO initiated, weight, and hours on ECMO.

	Survivors/ Expired *n* =	Survivors			Expired		
		Average age ECMO initiated in days	Average kilogram weight	Average hours on ECMO	Average age ECMO initiated in days	Average kilogram weight	Average hours on ECMO
All patients	172/38	14 ± 69*	3.5 ± 0.9†	138 ± 73‡	145 ± 698*	4.6 ± 5.3†	181 ± 155‡
Under 30 days (neonates)	163/31	2.4 ± 3.6§	3.4 ± 0.6¶	131 ± 58	4.4 ± 5.8§	3.3 ± 0.6¶	209 ± 155
30 days or greater	9/7	219 ± 228#	5.3 ± 2.5**	266 ± 170††	769 ± 1564#	10.3 ± 11.3**	62 ± 84††
By diagnosis		Age ECMO initiated in days range	Kilogram weight range	Hours on ECMO range	Age ECMO initiated in days range	Kilogram weight range	Hours on ECMO range
Adenovirus	2/1	0–1	3.8–4.0	88–201	8	3.5	563
Aspiration	1/0	37	4.5	161			
Adult respiratory distress syndrome	2/0	85–394	3.5–8.0	178–358			
Asphyxia	0/1				1	4.3	36
Foreign body aspiration	1/0	740	10.5	2			
Blood aspiration	3/0	0–3	2.8–4.0	88–141			
Gastroschesis (0%)	0/1				39	4.3	39
Group B *Streptococcus*	12/3	0–10	2.6–5.0	76–232	0–10	2.6–3.0	25–145
Hepatitis	0/1				1	3.4	307
Herpes	0/2				7–11	3.5–4.9	404–458
Hyperammonia	2/0	5–5	2.0–2.8	56–130			
Hyperviscosity syndrome	1/0	2	2.8	59			
Lymphatic dysplasia	0/1				2	3.5	149
Meconium aspiration	58/4	0–13	2.1–4.6	44–259	0–9	2.8–4.0	23–178
Perinatal acidosis	2/0	0–1	3.3–3.8	74–187			
Pertussis	0/1				24	3.6	584
Pulmonary hypertension	34/6	0–12	2.8–5.7	61–241	1–10	2.3–3.8	122–355
Pleural effusion	0/1				2	3.3	163
Pneumonia	12/1	1–75	2.7–4.3	63–356	7	3	285
Pulmonary hypoplasia	4/5	0–3	3.4–4.2	81–185	0–2	2.7–4.2	24–305
Respiratory distress syndrome	17/1	1–8	2.5–4.8	23–136	1	3.3	230
Respiratory syncytial virus	4/4	29–145	3.5–6.2	194–516	20–266	2.5–5.4	9–376
Sepsis	17/4	0–304	2.5–4.0	43–420	0.320	3.2–12.0	10–185
Sickle cell crisis	0/1				4310	35	79

All patients: Survivors vs. expired
*Age $p = .0157$
†Weight $p = .0133$
‡ECMO Hours $p = .0091$

Under 30 days: Survivors vs. expired
§Age $p = .0122$
¶Weight $p = .3388$
ECMO Hours $p < .0001$

30 days or greater: Survivors vs. expired
#Age $p = .3117$
**Weight $p = .2196$
††ECMO Hours $p = .0114$

Two hundred and ten patients with 24 separate primary diagnoses were reviewed. Statistical comparison confirms that expired neonatal patients (<30 days old) are placed on ECMO an average of 2 days later than survivors from the date of birth.

$$\text{Venoarterial } CO_2 \text{ gradient} = pvCO_2 - paCO_2$$

The first INDEX was calculated using the following formula (12):

$$\text{First INDEX} = \text{first AGc} + \text{first p[v – a] } CO_2.$$

Data Analysis

All data were recorded on a Microsoft Excel spreadsheet (Microsoft Corporation, Redmond, WA) for creation of tables and figures. Data was then transferred for analysis to the Graphpad Instat® statistical package (version 3.01 for Windows 95/NT, GraphPad Software, San Diego, CA).

Continuous variables are expressed as averages and standard deviations. Categorical variables are summarized with frequencies and percentages, except for the receiver operating characteristic derivatives which are shown as fractions. The only specific outcome evaluated is survival to hospital discharge.

RESULTS

The study population contained 24 separate primary diagnoses, 194 neonates (age less than 30 days), and 16 pediatric patients (age equal to or greater than 30 days) with 172 surviving and 38 expiring; an overall survival of 82%. Among the neonates, expired patients were placed on ECMO an average of 4 days after birth. Surviving patients were placed

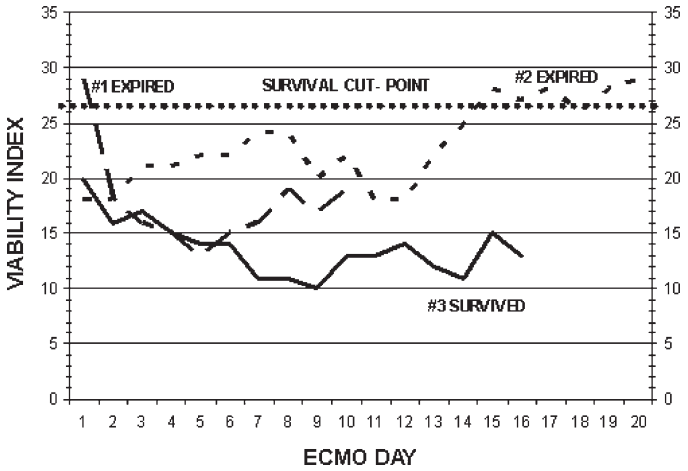

Figure 2. Examples of Daily Viability Index and survival. Patient #1 (long dashed line) had a moderate survival diagnosis (pulmonary hypertension: ~75% survival), but the Viability Index on the first ECMO day exceeded the hypothetical survival cut-point (dotted line). The remaining days on ECMO were all below the cut-point. Patient died of a large brain infarct. Patient #2 (short dashed line) had a low survival diagnosis (pertussis: ~30% survival). The Viability Index remained below the survival cut-point for the first 14 ECMO days, but then rose above the cut-point during the final week on ECMO. Patient died of multi-system organ failure, the pulmonary disease never having improved. Patient #3 (solid line) had a moderate survival diagnosis (sepsis: ~75% survival). The Viability Index during ECMO never exceeded the hypothetical survival cut-point. Patient survived without complications.

on ECMO an average of only 2 days after birth; $p < .05$ (Table 1). There was no data available to determine if the 2 day delay was caused by the failure of other therapies, by advanced morbidity, or some other cause such as transport delay. However, expired neonates had significantly higher first AGc values, higher first p[v-a] CO_2 values, and higher first INDEX values than surviving neonates, implying they were sicker when finally placed on ECMO. This was true of the older patients as well (Table 2).

Figures 3, 4, and 5 are frequency histograms for the first AGc, the first p[v-a]CO_2, and the first INDEX values. These histograms identify the specific cut-points where mortality greatly increases. The patients with a first AGc value ≥23 mEq/L, a first p[v-a]CO_2 value ≥16 mmHg, and a first INDEX ≥28 had a significantly higher mortality than patients with lower scores (Table 3). Patients with values below the cut-points had a survival average of 84% or better and patients with values above the cut-points had a survival average of 43% or less (Figure 6). Patients with values above the cut-points are much more likely to expire than patients with lower values; $p < .05$ (Table 4)

Figure 7 shows the survival percentage for the INDEX <28 and ≥28 by age; <30 days (neonates) and ≥30 days. Neonates with a first INDEX value ≥28 had an average survival rate of only 50% which constitutes a mortality rate over three times higher than neonatal patients with lower first INDEX values ($p < .05$). Older patients with a first INDEX ≥28 had an average survival rate of only 20%

Table 2. Respiratory ECMO patients: Survivors vs. expired patients.

	Mean ± SD	Mean ± SD	*t* Test *p*
	All patients		
	Survivors (n = 172)	Expired (n = 38)	
First adjusted anion gap	14 ± 4.0	16.5 ± 6.4	.0028
First venoarterial CO_2 gradient	6.7 ± 2.8	8.6 ± 5.1	.0020
First Viability Index	20.7 ± 4.4	25 ± 8.6	<.0001
	Patients < 30 days old		
	Survivors (n = 163)	Expired (n = 31)	
First adjusted anion gap	14.1 ± 4.0	16.2 ± 6.4	.0164
First venoarterial CO_2 gradient	6.6 ± 2.7	7.6 ± 4.2	.0718
First Viability Index	20.6 ± 4.3	23.8 ± 7.8	.0015
	Patients ≥ 30 days old		
	Survivors (n = 9)	Expired (n = 7)	
First adjusted anion gap	13.0 ± 4.2	17.7 ± 6.6	.1033
First venoarterial CO_2 gradient	9.1 ± 3.1	12.6 ± 6.8	.1916
First Viability Index	22.0 ± 5.4	30.3 ± 10.3	.0055

The first adjusted anion gap, the first venoarterial carbon dioxide gradient, and the first Viability Index are correlated to survival. The first Viability Index has greater correlation to survival than the other two markers in both neonates and older children.
SD, standard deviation.

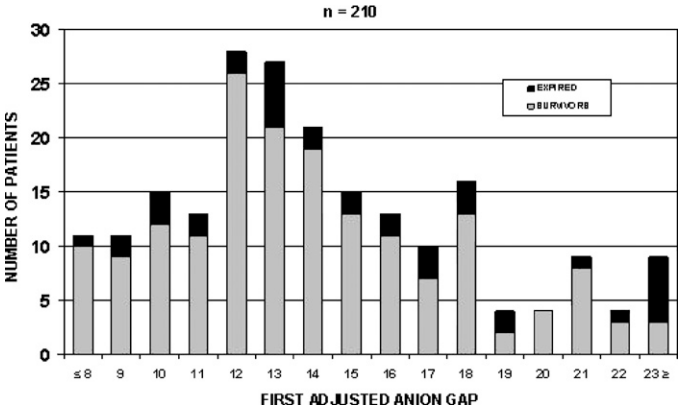

Figure 3. Respiratory ECMO patients: First adjusted anion gap frequency histogram. Two hundred and ten survivors and expired patients. "≤8" indicates all patients with values 8 or less, "≥23" indicates all patients with values 23 or greater. The cut-point for survival falls between 22 and 23 mEq/L.

which is also a mortality rate over three times higher than older patients with lower first INDEX values (although this does not reach statistical significance likely due to the small number of pediatric patients reviewed).

The first AGc and the first p[v-a]CO_2 each identified certain patients as being high risk (Table 3). Unfortunately, the first AGc only identified nine of the 210 ECMO patients as high risk and the first p[v-a]CO_2 only identified seven of the 210 ECMO patients as high risk. In contrast, the first INDEX identified 21 of the 210 ECMO patients as high risk; the sensitivity and specificity being higher for the

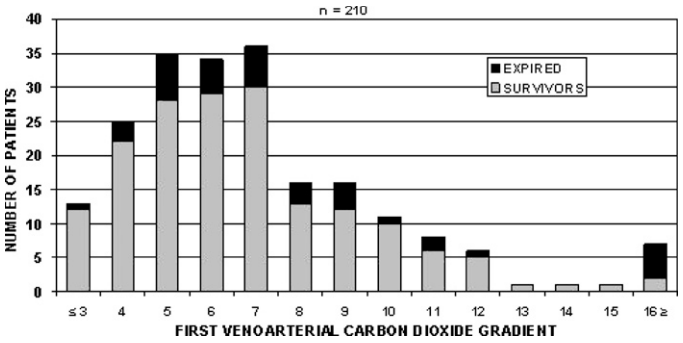

Figure 4. Respiratory ECMO patients: First venoarterial carbon dioxide gradient frequency histogram. Two hundred and ten survivors and expired patients. "≤3" indicates all patients with values 3 or less, " ≥16" indicates all patients with values 16 or greater. The cut-point for survival falls between 15 and 16 mmHg.

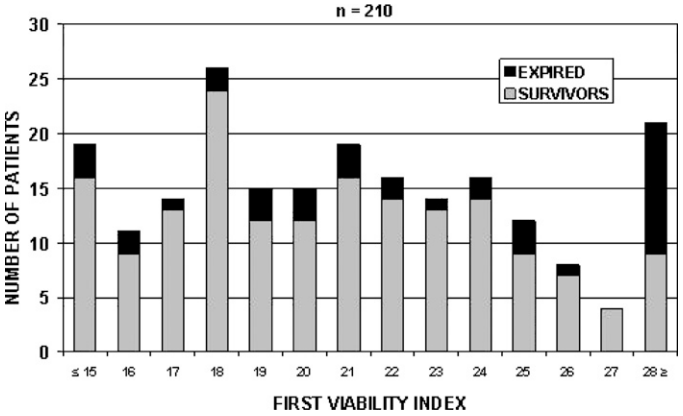

Figure 5. Respiratory ECMO patients: First Viability Index frequency histogram. Two hundred and ten survivors and expired patients. "≤15" indicates all patients with values 15 or less, "≥28" indicates all patients with values 28 or greater. The cut-point for survival falls between 27 and 28.

Table 3. Survival below and above the cut-points and Fisher's exact test.

	1st Adjusted Anion Gap < 23 mEq/L	1st Adjusted Anion Gap ≥ 23 mEq/L	Total
Survivors	169 (80%)	3 (1%)	172 (82%)
Expired	32 (15%)	6 (3%)	38 (18%)
Total	201 (96%)	9 (4%)	210 (100%)
		$p = .0014$	
	1st venoarterial carbon dioxide gradient < 16 mmHg	1st venoarterial carbon dioxide gradient ≥ 16 mmHg	Total
Survivors	170 (81%)	2 (1%)	172 (82%)
Expired	33 (16%)	5 (2%)	38 (18%)
Total	203 (97%)	7 (3%)	210 (100%)
		$p = .0024$	
	1st Viability Index < 28	1st Viability Index ≥ 28	Total
Survivors	163 (78%)	9 (4%)	172 (82%)
Expired	26 (12%)	12 (6%)	38 (18%)
Total	189 (90%)	21 (10%)	210 (100%)
		$p = .0001$	

Contingency tables showing a significant statistical difference for survival between patients below and above the cut-points or all three markers.

INDEX (Table 4). Generally, any AGc elevated above the highest normal value usually indicates that the tissues are experiencing some degree of hypoxia (13). Any p[v-a]CO_2 above the highest normal value indicates that the tissues are experiencing some degree of carbon dioxide retention (15). Moderately elevated AGc values or moderately elevated p[v-a]CO_2 by themselves are not necessarily lethal. Vital tissues seem to tolerate one or the other up to a certain cut-point: <16 mmHg for the p[v-a]CO_2 and <23 mEq/L for the AGc (Figures 3 and 4). However, if both indicators are moderately elevated (even to levels less than the cut-points), vital tissues seem to be less capable of tolerating both the effects of hypoxia and carbon dioxide retention simultaneously. These effects are apparently cumulative which explains the need to monitor the INDEX. The INDEX measures the extent of this combined effect which reaches its lethal tipping point at 28 (Figure 5). For example, one patient had a first AGc of 19 mEq/L and a first p[v-a]CO_2 of 11 mmHg; both values below the cut-points. However, the INDEX value was 30, which exceeds the cut-point. Patients with an INDEX of 30 or greater had a survival rate of only 38%. The likelihood ratio for survival is at least two times greater for patients below the cut-points and the likelihood ratio for death is over four times greater for those patients above the cut-points (Table 4).

DISCUSSION

This analysis supports the hypothesis that if the first Viability Index on ECMO is elevated beyond a certain cut-point, then the survival of neonatal and pediatric respiratory patients will be greatly diminished. The best window of opportunity to implement ECMO might be missed if only the AGc or only the p[v-a]CO_2 is monitored because the INDEX is superior at identifying patients at risk due to its greater specificity than the other markers (Figure 8).

Patients with a first INDEX value ≥28 probably have a higher mortality because the AGc detects tissue anoxia and the p[v-a]CO_2 detects carbon dioxide accumulation at the micro-vascular tissue level, both of which are caused by poor capillary perfusion (16). Together these risk markers detect tissues with localized hypoxic ischemia, which is caused by various types and degrees of shock. Vital tissues may tolerate an unspecified period of hypoxic ischemia without immediately appearing damaged. But this type of situation is the precursor needed to produce reperfusion injury once capillary perfusion is normalized, as occurs when ECMO begins (17). In the evolving acidic intracellular milieu of the ischemic tissues, the protective enzymatic antioxidants are deactivated (18). Upon the restoration of normal perfusion, the tissues are suddenly re-oxygenated and subsequently damaged by the uncontrolled reactive oxygen species before the antioxidants can be reactivated,

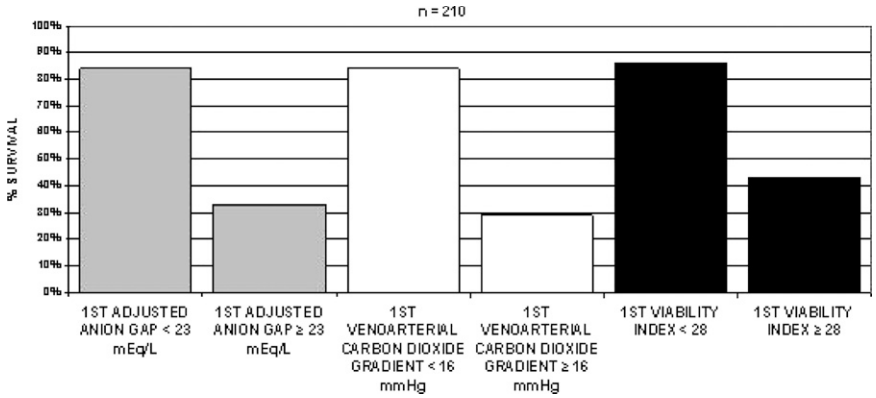

Figure 6. Respiratory ECMO patients: Average survival below and above the cut-points. One hundred and eighty nine survivors out of a total of 210 patients. The average survival by percentage below and above all three cut-points.

Table 4. Receiver operating characteristic derivations.

	1st Adjusted Anion Gap		1st Venoarterial Carbon Dioxide Gradient		1st Viability Index	
Derivative	<23 mEq/L: Predicting survival	≥23 mEq/L: Predicting death	<16 mmHg: Predicting survival	≥16 mmHg: Predicting death	<28: Predicting survival	≥28: Predicting death
Sensitivity	.84	.67	.84	.71	.86	.57
Specificity	.67	.84	.71	.84	.57	.86
Positive predictive value	.98	.16	.99	.13	.95	.32
Negative predictive value	.16	.98	.13	.99	.32	.95
Likelihood ratio	2.52	4.19	2.93	4.39	2.01	4.15
Accuracy	.83		.83		.83	
p	.0014		.0024		.0001	

Comparison of predictive power for survival below and death above the three cut-points. Derivations are calculated from values in Table 3. Sensitivity is the true positive rate in predicting the outcome. Specificity is the true negative rate in predicting the outcome. Positive predictive power (precision) = true positive rate/(true positive rate + false positive rate). Negative predictive power = true negative rate/(true negative rate + false negative rate). The likelihood ratio = sensitivity/(1.0-specificity). Accuracy = (true positive prediction + true negative prediction)/total population. The likelihood for survival is at least two times greater for patients below the cut-points. The likelihood of death is over four times greater for those patients above the cut-points.

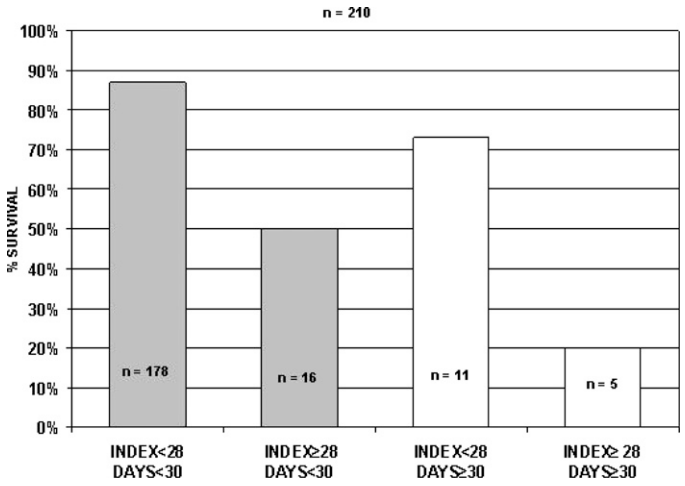

Figure 7. Respiratory patients by age. One hundred and eighty-nine survivors out of a total of 210 patients. First Viability Index vs. survival: "≤27, AGE <30 DAYS" indicate neonates with Viability Index values 27 or less. "≥28, AGE <30 DAYS" indicate neonates with Viability Index values 28 or greater. "≤27, AGE >30 DAYS" indicates older patients with Viability Index values 27 or less. "≥28, AGE >30 DAYS" indicates older patients with Viability Index values 28 or greater.

among other things (19–22). The damage caused by this pump-induced reperfusion injury, combined with the already present pathology, greatly increases the mortality.

In our population, expired neonates tend to be placed on ECMO later and have higher markers than surviving neonates. This may be due to a variety of causes. However, intervening with ECMO before the INDEX value exceeds 27 may avoid the added morbidity of reperfusion injury damage and result in a higher survival rate. If it is too late for optimal intervention with ECMO (i.e., the INDEX exceeds 27), then a different kind of pump strategy that deals with the various damaging aspects of reperfusion injury should be considered (23).

The first INDEX value of 27 is the specific cut-point beyond which the odds of survival are greatly reduced. The implication is that if the patient is placed on ECMO before the INDEX value reaches 28, the odds of survival will be improved. Ten percent of all the patients placed on ECMO in this review had a first INDEX value ≥28, suggesting that these 21 patients were placed on ECMO too late for optimal survival. Only nine of the 21 survived (43%). Lower

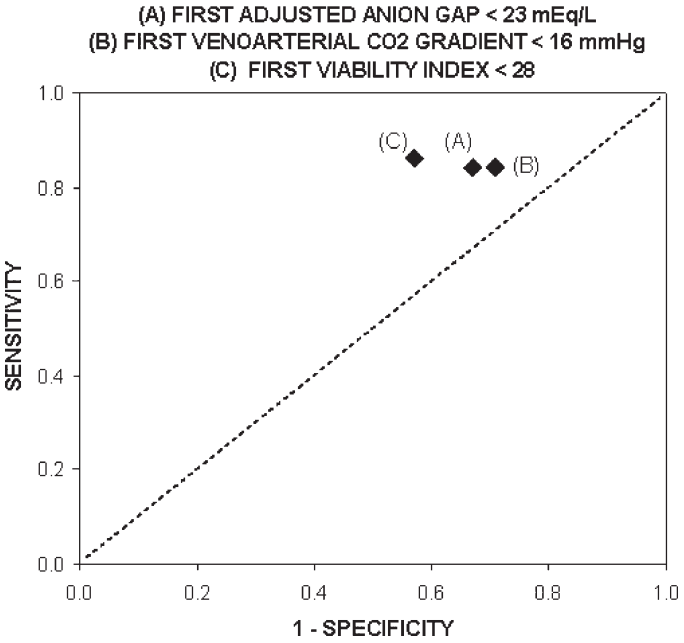

Figure 8. Receiver operating characteristic. The first Viability Index has better specificity than the first adjusted anion gap or the first venoarterial carbon dioxide gradient. This means that the Viability Index can identify additional patients as high risk even though they may not exceed either or both of the other two cut-points.

score patients had an average survival rate of 86%, which is an absolute risk reduction of 43% and a relative risk reduction of 50% over higher score patients. The number needed to treat among higher INDEX value patients (by using earlier intervention) to realize improved survival would only be 2.3.

The authors suggest that the clinical utility of an INDEX value drawn prior to ECMO implementation is limited to identifying patients at enhanced risk for tissue injury and to guiding the need for implementation of strategies to limit reperfusion injury such as more timely intervention or possibly therapeutic hypothermia. This data would not support the use of this identifier to limit care or therapy for an individual patient.

The limitations of this review are related to its retrospective design, covering two decades, and changes that have occurred in management during that time period. These may alter outcomes and are difficult to evaluate in a retrospective analysis. However, future prospective validation of these risk identifiers may lead to additional hypotheses that could identify therapies or treatment strategies which would be useful for reducing mortality or decreasing the effects of reperfusion injury.

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