clinical investigations in critical care

Prognostic Value of Extravascular Lung Water in Critically Ill Patients*

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Objective: **Measurement of extravascular lung water (EVLW) as a clinical tool for the assessment of pulmonary function has been found to be more appropriate than oxygenation parameters or radiographic techniques. In this study, we analyzed the prognostic value of EVLW in critically ill patients.**
Design: **Retrospective analysis.**
Setting: **Operative ICU of a university hospital.**
Measurements and results: **We retrospectively analyzed 373 critically ill patients (133 female and 240 male patients; age range, 10 to 89 years; mean ± SD age, 53 ± 19 years) who were treated in our ICU between 1996 and 2000. All these patients were hemodynamically monitored by the transpulmonary double-indicator (thermo-dye) dilution technique. Each patient received a femoral artery sheath through which a 4F flexible catheter with an integrated thermistor and fiberoptic was advanced into the infradiaphragmatic aorta. EVLW was calculated using a computer system. For each measurement, 15 to 17 mL of cooled 2% indocyanine green were injected central venously. In our results, maximum EVLW was significantly higher in nonsurvivors (n = 186) than in survivors (n = 187) [median, 14.3 mL/kg vs 10.2 mL/kg, respectively; $p < 0.001$]. In univariate logistic regression models, EVLW ($r^2 = 0.024$, $p = 0.003$) at baseline as well as simplified acute physiology score (SAPS) II ($r^2 = 0.135$, $p < 0.0001$) and APACHE (acute physiology and chronic health evaluation) II scores ($r^2 = 0.050$, $p < 0.0001$) were significant predictors of mortality. If SAPS II and APACHE II scores are combined, r^2 increases to 0.136, but the improvement over SAPS II alone is not significant. The addition of baseline EVLW further increases r^2 to 0.149 ($p = 0.021$ for the improvement), indicating that EVLW contributes independently to prognosis.**
Conclusion: **EVLW correlated well with survival (*ie*, nonsurvivors had significantly higher EVLW values than survivors) and is an independent predictor of prognosis.**
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Key words: indicator dilution; mortality; multiple organ failure; pulmonary function; sepsis

Abbreviations: APACHE = acute physiology and chronic health evaluation; AUC = area under the curve; EVLW = extravascular lung water; ICG = indocyanine green; ROC = receiver-operating characteristics; SAPS = simplified acute physiology score; SOFA = sepsis-related organ failure assessment

In many critically ill patients, it is a primary goal of treatment to restore and maintain organ perfusion, for which an adequate cardiac preload is required.[1] In achieving this, those patients are put at high risk of acquiring pulmonary edema due to potentially leaky capillaries,[2] so fluid management inthese patients is often a balancing act between avoiding pulmonary edema, while maintaining a sufficient intravascular volume for adequate cardiac preload. However, clinical assessment of the extent

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of pulmonary capillary leakage and pulmonaryedema is difficult. Several years ago, the transpulmonary double-indicator dilution technique was introduced for the measurement of extravascular lung water (EVLW).[3,4] Thermo-dye dilution is the approach most commonly used, in which a freely diffusible indicator ("cold") and a plasma-bound indicator (indocyanine green [ICG]) are injected simultaneously. This technique has been extensively validated in animal experiments using gravimetry[3,5] and in humans using radionuclide techniques.[6] Although known for many years, measurement of EVLW became possible at the bedside by a fiberoptic-based catheter system,[4,7] and has been found to be a clinically useful tool. However, this technique is relatively expensive and time-consuming; therefore, assessment of EVLW is increasingly performed by single transpulmonary thermodilution, which according to animal experimental and clinical data, is sufficiently accurate for the estimation of EVLW.[8,9]

Pulmonary edema is assessed by clinical tools, such as oxygenation indexes and chest radiographic techniques. While the EVLW is more sensitive than chest radiography or oxygenation indexes for detecting edema development,[10,11] pulmonary artery occlusion pressure as a surrogate for pulmonary capillary hydrostatic pressure has been shown to be a poor indicator of edema formation in patients with noncardiac pulmonary edema.[12] Since there are only a few number of studies on the prognostic value of EVLW measurement, we analyzed the prognostic value of EVLW in a large number of critically ill surgical patients.

Materials and Methods

We retrospectively analyzed data from 373 critically ill patients (133 female and 240 male patients; age range, 10 to 89 years; mean ± SD age, 53 ± 19 years; median, 57 years) who were treated in our ICU between 1996 and 2000. ICU admission diagnosis was sepsis/septic shock according to the criteria of the American College of Chest Physicians/Society of Critical Care Medicine consensus conference[13] (n = 193), ARDS (n = 49), severe head trauma (n = 48), intracranial hemorrhage (n = 55), and hemorrhagic shock (n = 28). Severity of disease on ICU admission was described by an averaged simplified acute physiology score (SAPS) II[14] of 70 ± 17 (median, 68) and APACHE (acute physiology and chronic health evaluation) II score[15] of 30 ± 6 (median, 29). Overall, patients' mean sepsis-related organ failure assessment (SOFA) score[16] was 13 ± 3 (median, 13). All patients were sedated, intubated, and receiving mechanical ventilation. According to clinical decision, patients underwent extended hemodynamic monitoring by the transpulmonary double-indicator (thermo-dye) dilution technique. Approval by our institutional board was obtained previously. Each patient received a 4F flexible aortic catheter with an integrated thermistor and fiberoptic (Pulsiocath 4F, PV 2024 L; Pulsion Medical Systems; Munich, Germany) that was advanced from a femoral sheath. For each injection, 15 to 17 mL of a cooled solution of ICG (Pulsion Medical Systems) dissolved in glucose 5% in a concentration of 2 mg/mL were used for central venous injection (triple-lumen central venous catheter, Certofix Trio; Braun; Melsungen, Germany). For triplicate measurement of cardiac output, the ICG injection was followed by two bolus injections of cooled saline solution. EVLW was calculated using a computer system (COLD-Z021; Pulsion Medical Systems).[4] By using these data, we previously validated single transpulmonary thermodilution for estimation of EVLW.[9]

Statistical Analysis

Statistical analysis for EVLW in survivors (n = 187) and in nonsurvivors (n = 186) was based on the highest value of EVLW in each individual. All values are given as mean ± SD. Box-plot descriptive statistics, Mann-Whitney *U* test, and χ^2 tests with Yates correction were made using software (SPSS for Windows 9.0; SPSS; Chicago, IL). Statistical significance was considered at $p < 0.05$. For the determination of receiver-operating characteristics (ROC) curves and comparison between different ROC curves, we used MedCalc (Version 4.16e for Windows 3.1; MedCalc Software; Mariakerke, Belgium).

The prognostic capacity of EVLW in comparison as well as in addition to baseline SAPS II and APACHE II scores was studied using a series of logistic regression models with the outcome "death." The prognostic capacity was measured using the r^2 of Cox and Snell.[17] Different models were compared by likelihood ratio tests. These analyses were performed without as well as with adjustment for diagnostic groups, since mortality rates differed between diagnoses. In order to evaluate the use of baseline EVLW as potential future predictor, for each diagnostic group as well as for the complete study population, optimal cutoffs were derived from ROC analyses.[18]

Results

Demographic data and patients' characteristics are summarized in Table 1. In our results, maximum EVLW was significantly higher in nonsurvivors than in survivors (15.6 ± 7.8 mL/kg [median, 14.3 mL/kg] vs 12.2 ± 6.4 mL/kg [median, 10.2 mL/kg], respectively; $p < 0.001$) [Fig 1]. Patients with ARDS (n = 49) had a significantly higher EVLW (median, 14.9 mL/kg) than all other patients (n = 324) [median, 11.9 mL/kg], respectively ($p < 0.05$). Furthermore, patients with neither sepsis nor ARDS had significantly lower highest EVLW values (median, 9.2 mL/kg) when compared with both other groups ($p < 0.05$).

By separating several ranges of highest EVLW, the analysis indicates significantly increasing mortality with higher EVLW. In detail, mortality was approximately 65% in patients with EVLW > 15 mL/kg, and survival was approximately 67% in patients with EVLW < 10 mL/kg (Fig 2). The analysis of three different subgroups of patients (sepsis, ARDS, and all others) showed that within the sepsis group, nonsurvivors had significantly higher EVLW than survivors. In detail, mean EVLW for survivors vs nonsurvivors was 14.5 mL/kg vs 9.1 mL/kg for the

Table 1—*Study Data

Variables	Survivors (n = 187)	Nonsurvivors (n = 186)
Female/male gender	69/118	64/122
Age, yr‡		
Range	10–89	10–88
Mean ± SD	47 ± 19	59 ± 18
Median	49	62
SAPS II‡		
Range	35–108	30–116
Mean ± SD	63 ± 13	75 ± 17
Median	61	73
APACHE II‡		
Range	13–41	14–48
Mean ± SD	28 ± 5	31 ± 6
Median	28	30
SOFA‡		
Range	5–20	5–21
Mean ± SD	12 ± 3	14 ± 3
Median	12	14
Sepsis	64	129
ARDS	27	22
Severe head trauma	37	11
Intracranial hemorrhage	40	15
Hemorrhagic shock	19	9
Extended monitoring, d†		
Range	1–43	1–49
Mean ± SD	7 ± 6	9 ± 8
Median	5	7
ICU stay, d‡		
Range	1–121	0–126
Mean ± SD	24 ± 17	17 ± 20
Median	20	11

*Data are presented as No. unless otherwise indicated.
†Significantly different between both groups ($p = 0.01$), Mann-Whitney *U* test.
‡Significantly different between both groups ($p < 0.0001$), Mann-Whitney *U* test.

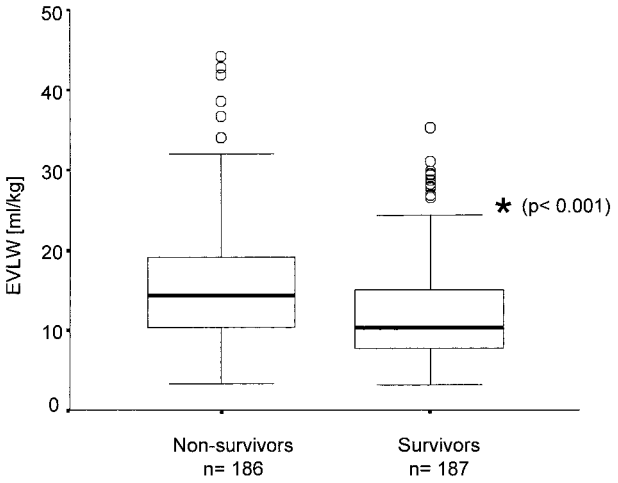

FIGURE 1. Box plot for survivors and nonsurvivors. Bold lines indicate medians, box plots indicate 25 to 75th percentiles, and bars indicate the 1.5-fold of the whole box length. Circles indicate values between 1.5-fold to threefold of the whole box length, and outliers (outside threefold of the whole box length) are indicated by asterisks. The bold asterisk indicates statistical significance (Mann-Whitney *U* test).

subgroup sepsis, 18.2 mL/kg vs 15.8 mL/kg for the subgroup ARDS, and 10.5 mL/kg vs 9.1 mL/kg for the subgroup of all others, respectively (Fig 3).

ROC statistics using the highest EVLW value in each individual revealed an area under the curve (AUC) of 0.649 with a cutoff point of > 9.2 mL/kg (Fig 4). In 211 of the 336 patients (57%), the first EVLW measurement was made within 24 h after admission to the ICU. Since scores of severity of illness are only validated for the first 24 h after ICU admission, we compared APACHE II score, SAPS II, SOFA score, and EVLW on ICU admission by ROC statistics. AUCs were 0.692 for APACHE II score, 0.766 for SAPS II, 0.756 for SOFA score, and 0.639 for EVLW, respectively (Fig 5). The comparison between AUCs for EVLW with SOFA ($p = 0.012$) and SAPS II score ($p = 0.008$) showed a statistically significant difference.

In univariate logistic regression models, EVLW ($r^2 = 0.024$, $p = 0.003$) at baseline as well as SAPS II ($r^2 = 0.135$, $p < 0.0001$) and APACHE II scores ($r^2 = 0.050$, $p < 0.0001$) were significant predictors of mortality. If SAPS II and APACHE II scores are combined, r^2 increases to 0.136, but the improvement over SAPS II alone is not significant. The addition of baseline EVLW further increases r^2 to 0.149 ($p = 0.021$ for the improvement), indicating that EVLW contributes independently to prognosis.

If maximum EVLW is added to the model, r^2 is further increased to 0.176 ($p = 0.002$ for the

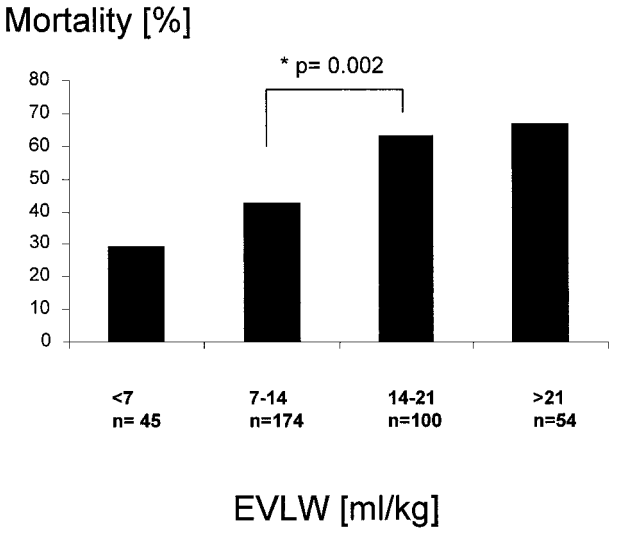

FIGURE 2. Mortality as a function of EVLW. Patients were classified into four groups according to their highest EVLW value. The asterisk indicates statistical significance to the next higher EVLW group (χ^2 test).

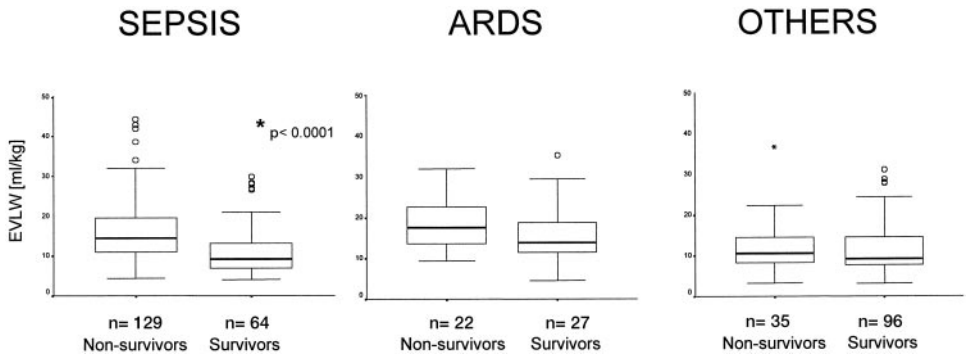

FIGURE 3. Box plot for the different subgroups of patients (*ie*, sepsis, ARDS, and all others). Bold lines indicate medians, box plots indicate 25 to 75th percentiles, and bars indicate the 1.5-fold of the whole box length. Circles indicate values between 1.5-fold to threefold of the whole box length, and outliers (outside threefold of the whole box length) are indicated by asterisks. The bold asterisk indicates statistical significance (Mann-Whitney *U* test).

improvement). Mortality varied with diagnosis ($r^2 = 0.131$, $p < 0.0001$). While 129 of the 193 septic patients (66.8%) died, mortality in patients with ARDS was 44.9% (22 of 49 patients), and in all other patients was 26.7% (35 of 131 patients). Even after adjustment for these diagnostic groups, baseline EVLW improved prognosis to $r^2 = 0.147$ ($p = 0.009$ for the improvement). No significant interaction was observed, indicating that the EVLW-associated mortality increase is comparable in all diagnostic groups. Even a model incorporating diagnostic group, SAPS II, and APACHE II score ($r^2 = 0.196$) could be improved significantly by EVLW ($r^2 = 0.206$, $p = 0.029$) and further improved by maximum EVLW ($r^2 = 0.223$, $p = 0.005$). ROC-based cutoffs varied only to a small extent between diagnostic groups. For the complete study population, a cutoff of > 6.5 mL/kg was derived, resulting in a sensitivity of 69.4% and a specificity of 50.8%.

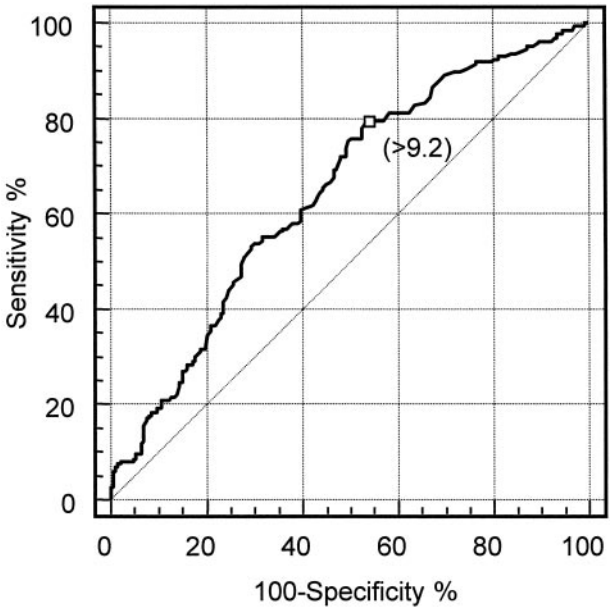

FIGURE 4. Sensitivity and specificity of highest EVLW value with respect to outcome according to ROC in 373 patients. The AUC was 0.649.

The mean time elapsed between ICU admission and highest EVLW value was 7.6 days. In this large sample of critically ill patients undergoing femoral artery cannulation, we observed only five patients who required surgical intervention due to occlusion of the vessel, peripheral embolization, or bleeding complications. No allergic reactions to ICG, which have been reported to occur with an incidence of 1:40,000,[19] were observed.

DISCUSSION

In our study, EVLW as marker of pulmonary function was found to be a good and independent predictor of survival in critically ill patients (*ie*, mortality increased with higher EVLW values and nonsurvivors had significantly higher EVLW values than survivors). Our data support the results as previously described by Sturm,[6] who studied 81 surgical patients after major abdominal surgery or multiple trauma. While in this population mortality was approximately 30% for patients with EVLW < 9 mL/kg, Sturm[6] clearly showed that mortality steeply increased when EVLW was > 9 mL/kg. The increase in mortality flattened with increasing EVLW, and mortality was approximately 80% in patients with EVLW > 20 mL/kg. In principle, EVLW was significantly higher in septic patients when compared to nonseptic patients.[6] We found comparable results (*ie*, the mortality rate was approximately 65% when EVLW was > 15 mL/kg).

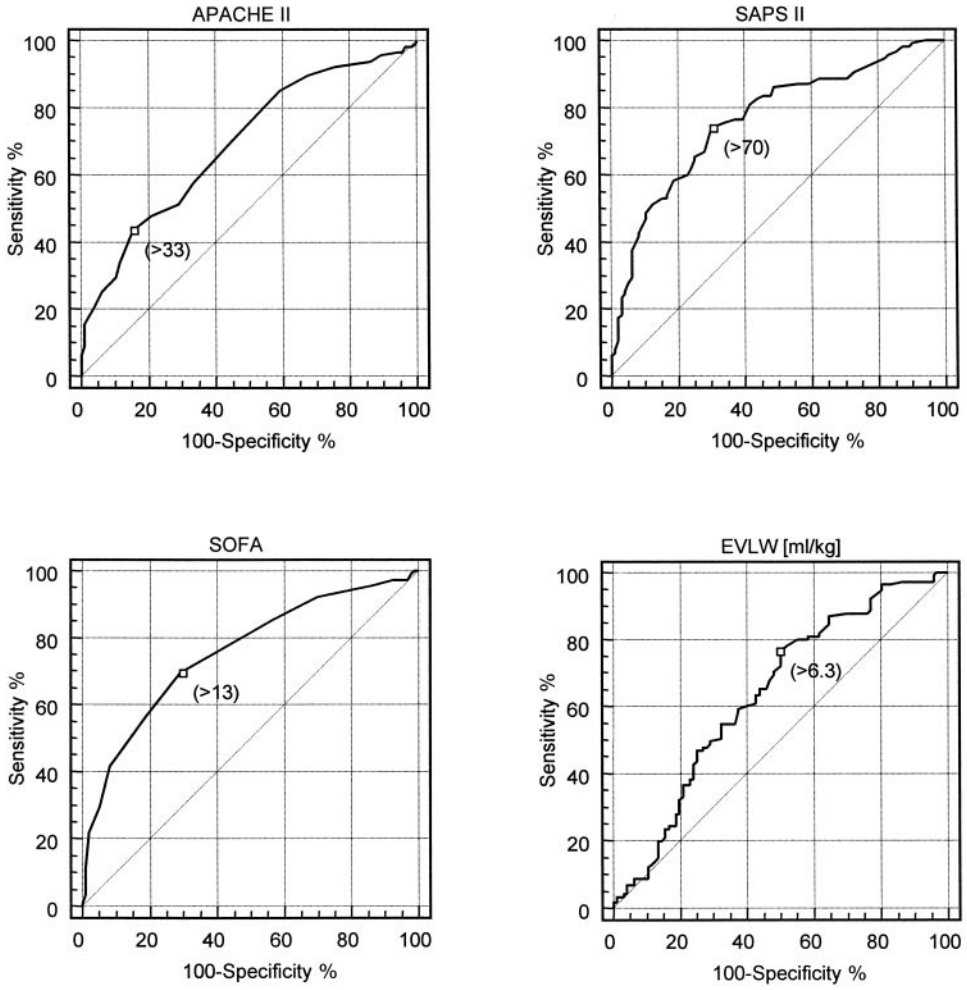

FIGURE 5. Sensitivity and specificity of ICU admission values for EVLW, SAPS II, APACHE II score, and SOFA score with respect to outcome according to ROC in 211 patients. The AUCs were 0.692 for APACHE II score, 0.766 for SAPS II, 0.756 for SOFA score, and 0.639 for EVLW, respectively. The comparison between AUCs for EVLW with SOFA score ($p = 0.012$) and SAPS II ($p = 0.008$) showed a statistically significant difference.

In our study, ROC-based cutoffs varied only to a small extent between diagnostic groups. For the complete study population, a cutoff of > 6.5 mL/kg was derived, resulting in a sensitivity of 69.4% and a specificity of 50.8%. This finding is not very impressive. Baseline EVLW should only be used in addition to other sources of information as diagnosis and SAPS II; however, it is more informative than an APACHE II score for prognosis.

The analysis on subpopulations of patients showed that only in the sepsis group, EVLW was significantly higher in nonsurvivors. Within the subgroup ARDS, only a tendency toward higher EVLW in nonsurvivors was found, which in part may be explained by the small number of patients. By definition, patients with ARDS have a *per se* increased EVLW, and mortality may be even more determined by other organ function than EVLW. While increased EVLW in patients with sepsis may be regarded as predictive for survival, other patients may have died from other reasons than EVLW. Furthermore, EVLW on ICU admission as one single variable was found to be less accurate than more complex scores (*ie*, SOFA score and SAPS II) with respect to outcome prediction. However, a comparison between EVLW on ICU admission and APACHE II score did not show significant difference.

The scores are only validated for the first 24 h after admittance to the ICU. At this time point, SAPS II and SOFA scores have a higher sensitivity and specificity in terms of outcome than EVLW. However, it should be emphasized that EVLW is only a measure of one single organ system. More important, whenever the transpulmonary indicator dilution method (a well-founded technique[20–22]) is applied in the clinical setting, EVLW as an organ function

parameter has a relevant predictive value during the further course. One might speculate that therapeutic strategies to reduce EVLW are indeed beneficial in terms of outcome.

Previously, Sturm et al[23] found EVLW to be correlated with albumin extravasation in patients after multiple trauma, while other parameters of oxygenation failed to indicate pulmonary deterioration. Measurement of EVLW has been shown to be helpful in changing respirator therapy from a controlled- to an assisted-breathing mode.[24] Using EVLW to guide the management of patients with both cardiac and noncardiac pulmonary edema (ARDS) has been shown to reduce the duration of mechanical ventilation, length of stay in the ICU,[25] and potential intensive care costs. EVLW-guided therapy also reduced mortality in those patients with congestive heart failure and ARDS.[26] Thus, bedside measurement of EVLW seems to be an appropriate approach for monitoring and management of patients at risk of pulmonary edema formation.

Moreover, EVLW seems to be of value during patient's course because maximum EVLW improves prediction (*ie*, maximum EVLW that developed during the course was found to be better in predicting mortality). While this finding emphasizes the association of EVLW and death, maximum EVLW is not known before observation ends and thus practically cannot be used for early prognosis.

In general, the transpulmonary double-indicator dilution technique has several potential limitations, as has been shown in the experimental setting. In a dog model, Gray et al[27] found that the transpulmonary thermo-dye technique has difficulties in detecting pulmonary edema in lung zones that are not perfused or only less perfused. The same group[28] showed in animals with chemically induced pulmonary edema that EVLW was underestimated due to distribution of pulmonary blood flow away from edematous areas. Despite these potential limitations, transpulmonary indicator dilution technique may be considered useful since it allows clinical measurement of EVLW in critically ill patients at the bedside.

In conclusion, EVLW was found to correlate with survival in critically ill patients (*ie*, nonsurvivors had significantly higher EVLW values than survivors). Although the predictive value of EVLW for the first 24 h after admission to the ICU is worse than that of established scores, EVLW as a marker of a single organ function is an independent predictor of outcome that has a predictive value also during the further course. Therefore, measurement of EVLW seems valuable for the clinical setting, particularly since single transpulmonary thermodilution has been shown to be sufficiently accurate for the estimation of EVLW.

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