Association between Different Indexations of Extravascular Lung Water (EVLW) and PaO2/FiO2: A Two-Center Study in 231 Patients

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Abstract

Background: Variability of body weight (BW) and height calls for indexation of volumetric hemodynamic parameters. Extravascular lung water (EVLW) has formerly been indexed to actual BW (BWact) termed EVLW-index (EVLWI). In overweight patients indexation to BWact might inappropriately lower indexed EVLWIact. Several studies suggest indexation of EVLWI to predicted BW (EVLWpred). However, data regarding association of EVLWIact and EVLWpred to mortality and PaO2/FiO2 are inconsistent. Two recent studies based on biometric database-analyses suggest indexation of EVLWI to height (EVLWIheight). Therefore, our study compared the association of un-indexed EVLW, EVLWIheight, EVLWpred and EVLWIact to PaO2/FiO2 and Oxygenation index (OI = mean airway pressure*FiO2*/PaO2).

Methods: A total of 2119 triplicate transpulmonary thermodilutions (TPTDs; PiCCO; Pulsion Medical-Systems, Germany) were performed in 50 patients from the evaluation, and 181 patients from the validation groups. Correlations of EVLW and EVLWI to PaO2/FiO2 were performed. In the evaluation group, un-indexed EVLW (AUC 0.758; 95%-CI: 0.637–0.880) and EVLWIheight (AUC 0.746; 95%-CI: 0.622–0.869) provided the largest ROC-AUCs regarding PaO2/FiO2. The AUC for EVLWIact was smaller (0.713). EVLWIact provided the smallest AUC (0.685). This was confirmed in the validation group: EVLWIheight provided the largest AUC (0.735), EVLWIact (0.710) the smallest. In the merged data-pool, AUC was significantly greater for EVLWIheight (0.729; 95%-CI: 0.674–0.784) compared to all other indexations including EVLWIact (ROC-AUC 0.683, p = 0.007) and EVLWIpred (ROC-AUC 0.707, p = 0.015). The association of EVLWI was even stronger to OI compared to PaO2/FiO2. In the merged data-pool, EVLWIheight provided the largest AUC regarding “OI>10” (0.778; 95%-CI: 0.713–0.842) compared to 0.739 (95%-CI: 0.669–0.810) for EVLWIact and 0.756 (95%-CI: 0.688–0.824) for EVLWIpred.

Conclusions: Indexation of EVLW to height (EVLWIheight) improves the association of EVLW(I) to PaO2/FiO2 and OI compared to all other indexations including EVLWIact and EVLWIpred. Also considering two recent biometric database analyses, EVLWI should be indexed to height.

Introduction

Extravascular lung water (EVLW) is a measure of the interstitial, alveolar and lymphatic fluid content of the lungs. EVLW and its indexation to body weight (EVLWI) became routinely available after the introduction of single-indicator transpulmonary thermodilution (TPTD) [1–5]. A number of animal and clinical studies demonstrated an association of EVLWI to mortality and to parameters of pulmonary function such as PaO2/FiO2 [5–19]. Variability of body weight (BW) and height strongly...
calls for biometric adjustment and indexation. Ideally, appropriate indexation should be based on a limited number of routinely available biometric data, and it should result in consistent normal values for patients with different height, weight, age, gender and race [20–21]. Originally actual body weight (BW<sub>act</sub>) was used for indexation of EVLW. However, triggered by a rapidly increasing number of obese patients [22, 23], the question arose as to which weight to choose for EVLW indexation since indexation to BW<sub>act</sub> might inappropriately decrease EVLWI<sub>act</sub> in obese patients. Based on a better correlation to mortality, a number of studies have suggested indexation of EVLW to predicted BW (EVLW<sub>pred</sub>) (see Table 1) [12: 14]. However, data are inconsistent regarding other endpoints: e.g. if available data provide worse [12], similar [14, 16] or slightly better correlation of EVLW<sub>pred</sub> to PaO<sub>2</sub>/FiO<sub>2</sub> than EVLWI<sub>act</sub> [13]. In one of the most recent studies [15], “Chew et al. found that EVLW indexed to absolute body weight resulted in a stronger association with outcome” including mortality compared to EVLWI<sub>pred</sub> [24]. Despite the overall strong predictive capacity of EVLW in this and other recent trials [12–19], these inconsistencies demonstrate the need to optimize indexation of EVLW. Therefore, we recently analyzed a prospectively maintained database regarding the association of EVLW to biometric data [19]. This study demonstrated that height was the only biometric parameter independently associated to EVLW. These data were recently confirmed by Wolf et al., using a similar approach in a surgical group [19]. Despite these conclusive data, both studies did not investigate, if indexation of EVLW to height (EVLWI<sub>height</sub>) provides better association to pulmonary function and outcome. Furthermore, all these trials were mono-centric. Therefore, this two-center study compared the association of PaO<sub>2</sub>/FiO<sub>2</sub> (and other outcome markers) to EVLW (un-indexed), EVLWI<sub>act</sub>, EVLWI<sub>pred</sub>, EVLWI<sub>height</sub> and EVLWI indexed to other biometric indices. To provide sufficient balance of biometric data, we investigated a group with a representative distribution of body mass index (BMI) [22], as well as an unselected second group from a second center.

Materials and Methods

Munich-evaluation-group

The institutional ethics committee approved the study (Ethikkommission Technische Universität München; Fakultät für Medizin; No. 3049/11). Patients on mechanical ventilation were included using TPTD regardless of the study were included in the prospectively maintained database. The need for informed consent was waived due to the non-interventional design of the study. The patients included in this study completely distinct to the group previously analysed regarding the association of EVLW to biometric data [18].

To provide a representative distribution regarding bodyweight [22], we included 15 consecutive patients with BMI $\geq$ 30 kg/m$^2$, 15 consecutive patients with 25 $\leq$ BMI $< 30$ kg/m$^2$ and 20 consecutive patients with a normal BMI (<25 kg/m$^2$) irrespective of fulfilling the criteria of acute respiratory distress syndrome (ARDS). Conscious patients were asked for actual biometric data. In unconscious patients body weight and height were extracted from the patients records. In case of doubt height was verified using a flexible tape measure in the supine position.

A 5-F thermistor-tipped femoral arterial line (PV2025L20, Pulsiocath, Pulsion Medical Systems, Munich, Germany) connected to the PiCCO monitor device (PiCCO-Plus; Pulsion Medical Systems) was used for TPTD measurements. The mean EVLW was measured based on TPTD performed in triplicate with 15 ml cold saline 0.9%.

Antwerp-validation-group

Retrospective analysis of data from a prospectively developed independent cohort was performed for the first 7 days of ICU admission. Data of 181 critically ill patients requiring mechanical ventilation and TPTD-hemodynamic monitoring treated in two ICU’s in ZNA Campus Stuivenberg, Antwerp, Belgium were collected prospectively. Ethics approval had been obtained and due to the retrospective analysis and non-interventional nature of the study the need for informed consent was waived (project number EC 3765; Commissie voor Medische Ethiek, Ziekenhuisnetwerk Antwerpen 2020). Parts of the data not related to EVLW-indexation have already been published in Annals of Intensive Care [25, 26].

The measuring technique was identical to the Munich-evaluation-group, with the only difference being that three 20 ml boluses of cooled saline were used for TPTD.

Mean length of the ICU-stay in the Munich group was 27.2 $\pm$ 21.4 days with a range of 3 to 120 days. In the Antwerp group the mean ICU stay was 25.9 $\pm$ 41.7 days with a range of 1 to 429 days.

### Table 1. Indexations of extravascular lung water (index) EVLW/EVLWI.

| Indexation | Formula | Description |
|------------|---------|-------------|
| EVLWI<sub>act</sub> | EVLW/BW<sub>act</sub> | Actual body weight |
| EVLWI<sub>pred</sub> | EVLW/BW<sub>pred</sub> | Predicted body weight |
| EVLWI<sub>ideal</sub> | EVLW/BW<sub>ideal</sub> | Ideal body weight |
| EVLWI<sub>adj</sub> | EVLW/BW<sub>adj</sub> | Adjusted body weight |
| EVLWI<sub>height</sub> | EVLW/height | Height |
| EVLWI<sub>BMI</sub> | EVLW/BMI | Body Mass Index (kg/m$^2$) |
| EVLWI<sub>TLC</sub> | EVLW/TLC | Total Lung Capacity (L) |

BMI = Body Mass Index (kg/m$^2$); BW<sub>act</sub> [kg]/[height[m]$^2$]; $0.007184^*weight$ [kg]$^{0.425}*height$ [cm]$^{0.725}$; $7.99^*height$ [m] – 7.08; 6.60$^*height$ [m] – 5.79; 6.60$^*height$ [m] – 5.79; $50^*height$ [cm] – 152.4; $45.5^*height$ [cm] – 152.4; $50^*height$ [cm] – 152.4; 0.85; 0.9; 0.91; 0.91; 0.85; 0.85

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Endpoints and Statistics

1) **Weight and weight-correction formula based indexations.** To compare the distribution of normal (EVLWI < 7 ml/kg), slightly elevated (7 ≤ EVLWI < 10 ml/kg) and markedly elevated EVLWI (EVLWI ≥ 10 ml/kg) in dependency of the indexation, un-indexed EVLWI was indexed according to actual (EVLWIact), predicted (EVLWIpred), ideal (EVLWIid) and adjusted BW (EVLWIadj) using the formulas mentioned in Table 1. The cut-offs of 10 ml/kg and 14 ml/kg have been demonstrated to be associated with ARDS [15] and mortality [5].

- **Intra-group comparisons:** For the weight-related indexations, intragroup comparisons of weight-correction based EVLWI were performed for all patients and the subgroups with BMI < 25 kg/m², 25 ≤ BMI < 30 kg/m² and BMI ≥ 30 kg/m² (Wilcoxon-test for unpaired samples; Table 2).

- **Inter-group comparisons:** Furthermore, we compared EVLWI according to all investigated indexations (also including EVLWIheight, EVLWI Phys, EVLWIBSA and EVLWI TlCc) between patients with BMI < 25 kg/m² and patients with BMI ≥ 30 kg/m² (Wilcoxon-test for unpaired samples; Table 2).

2) **Association of EVLWI(I) to PaO2/FiO2 and oxygenation index (OI = mean airway pressure * FiO2 * PaO2⁻¹).** For appropriate analysis of multiple serial measurements in 231 patients from the two groups several statistical analyses were performed:

2a.) **Prediction of critical thresholds of PaO2/FiO2 and oxygenation index:** The clinically relevant prediction of critical thresholds of “PaO2/FiO2 < 200 mmHg” (primary endpoint) and “O1 > 10” by EVLWI was investigated using receiver operating characteristics area under the curve (ROC-AUC) analyses of all measurements.

2b.) **Inter-individual (“between-subject”) correlations:** Furthermore, correlations of EVLWI and differently indexed EVLWI to PaO2/FiO2 and oxygenation index (OI = mean airway pressure * FiO2 * PaO2⁻¹) were calculated. Since multiple serial measurements within 241 different patients were available, we analysed inter- and intra-individual correlations.

To correct for different numbers of measurements for each patient, the means of EVLWI, PaO2/FiO2 and OI were calculated for each individual patient (“one point per patient”). Subsequently the correlations between EVLWI and PaO2/FiO2 and between EVLWI and OI were calculated.

2c.) **Intra-individual (“within subject”) correlations:** The above-mentioned “one point per patient” analyses reflect the **inter-individual association** of EVLWI(I) to PaO2/FiO2 and OI. However, in cases of multiple serial measurements within different patients, **between-subject heterogeneity** may obscure correlations on an individual level (within subject correlation) which might be even more interesting than the inter-individual association. The effect of the confounder (between-subject heterogeneity) can be removed by calculating “partial” correlation between EVLWI(I) and PaO2/FiO2 (or OI) adjusting for heterogeneity of different patients (individual patient number/identifier as the adjustment factor).

3) **Mortality analysis.** Better prediction of mortality by EVLW according to any indexation might be related to the direct association of the indexation to mortality. To overcome this problem, multiple binary logistic regression analysis regarding mortality included the first and last values of unindexed EVLW as well as BWact, height, gender and acute physiology and chronic health evaluation (version 2, APACHE-II).

All analyses were performed separately in both groups and in the merged data, with the only exceptions being intergroup-comparisons and mortality analyses which were restricted to the BMI-representative Munich-evaluation-group. Results of merged data were considered superior to those derived from sub-groups. No correction of p-values was applied to adjust for multiple testing. However, results of all statistical tests being conducted were thoroughly reported so that an informal adjustment of p-values can be performed while reviewing the data [27].

All statistical tests were conducted 2-sided and a p-value < 0.05 was considered to indicate statistical significance. The software used was IBM SPSS statistics, version 20.

Results

**Patients’ characteristics**

A total of 2119 TPTDs (each with triplicate TPTD) were performed in 231 patients from both groups.

Table 2 summarizes the patients’ characteristics of both groups.

1) **Weight and weight-correction formula based indexations.** Comparison of EVLWIact, EVLWIpred, EVLWId and EVLWIadj. Table 2 demonstrates that in the Munich-evaluation-group mean values of EVLWIpred, EVLWIadj and EVLWIid were significantly higher than EVLWIact in the subgroups of patients with BMI ≥ 30 kg/m² and with 25 ≤ BMI < 30 kg/m² as well as for the totality of patients (intra-BMI-group-comparison). By contrast, EVLWIact and EVLWIadj were significantly lower than EVLWIact in the subgroup of patients with a normal BMI.

Similarly, in the Antwerp-validation-group mean values of EVLWIpred, EVLWIadj and EVLWIid were higher than mean the EVLWIact.

**Impact of indexation according to different weight-correction-formulas for the classification of EVLWI:** Distribution of EVLWI-values classified as normal (EVLWI < 7 ml/kg), moderately elevated (7 ml/kg ≤ EVLWI < 10 ml/kg) and markedly elevated EVLWI (EVLWI ≥ 10 ml/kg) significantly varied among the patients with a BMI ≥ 30 kg/m² as well as in the total patient groups depending on the weight used for indexation of EVLWI (Fig. 1). For example, in patients with a BMI ≥ 30 kg/m², 51% (133/263) of EVLWIact measurements were within the normal range (EVLWI < 7 ml/kg). By contrast only 16% (43/263; p < 0.001 vs. EVLWIact), 14% (38/263; p < 0.001) and 30% of the measurements (79/263; p < 0.001) were within the normal range if EVLWI was indexed according to predicted, ideal and adjusted BW, respectively. In addition to the different distributions of EVLWI classifications, different indexations obviously had an impact on the coefficient of variation (COV), in particular in patients with a BMI ≥ 30 kg/m² (Table 2). COV amongst these
## Table 2. Patients' characteristics.

| Parameter                      | Munich-Evaluation-Group                      | Antwerp-Validation-Group                      |
|--------------------------------|----------------------------------------------|----------------------------------------------|
|                                | All patients | BMI < 25 kg/m² | 25 ≤ BMI < 30 kg/m² | BMI ≥ 30 kg/m² | All patients from Antwerp |
| **Gender**                     |              |                |                    |                |                           |
| 22 female, 28 male             | 6 female, 14 male | 7 female, 8 male | 9 female, 6 male | 62 female, 119 male |
| **Age**                        | 641 ± 14.8 years | 676 ± 14.3 | 62.5 ± 18.7 | 63.3 ± 11.2 | 62.4 ± 16.4 |
| **Weight**                     | 820 ± 23.5 | 639 ± 92 | 78.7 ± 12.2 | 105.1 ± 29.2 | 74.5 ± 17.6 |
| **Height**                     | 169 ± 10.1 | 169 ± 90 | 172 ± 13.0 | 169 ± 8.9 | 170 ± 11.6 |
| **Body mass index**            | 28.3 ± 6.7 | 220 ± 1.9 | 27.4 ± 13.3 | 35.9 ± 6.3 | 25.6 ± 5.5 |
| **APACHE II-Score**            | 24.9 ± 9.8 | 257 ± 8.6 | 23.2 ± 7.8 | 24.6 ± 9.2 | 22.9 ± 10.3 |
| **Etiology**                   |              |                |                    |                |                           |
| Sepsis                         | 21            | 11             | 3                  | 7              | - acute on chronic 11/181 |
| Pneumonia/ARDS                 | 11            | 3              | 3                  | 5              | - acute 152/181 |
| Liver cirrhosis/ARDS           | 7             | 3              | 3                  | 1              | - coma 18/181 |
| Pancreatitis                   | 4             | 1              | 2                  | 1              | Medical patients 158 |
| Other etiology                 | 7             | 4              | 4                  | 1              | Surgical patients 23 |

### Different Indexations of Extravascular Lung Water vs. PaO2/FiO2

| Parameter | Mean ± SD | Median; COV | Mean ± SD | Median; COV | Mean ± SD | Median; COV | Mean ± SD | Median; COV |
|-----------|-----------|-------------|-----------|-------------|-----------|-------------|-----------|-------------|
| EVLWI unindexed | 716 ± 363 | 637; 0.51 | 711 ± 266 | 700; 0.37 | 618 ± 270 | 560; 0.44 | 783 ± 469 | 660; 0.60 | 773 ± 346 | 683; 0.45 |
| EVLWI<sub>un</sub> | 8.9 ± 3.8 | 8; 0.43 | 11.2 ± 3.7 | 11; 0.33 | 7.7 ± 3.1 | 7; 0.40 | 7.4 ± 3.0 | 6; 0.41 | 10.6 ± 4.7 | 10; 0.44 |
| EVLWI<sub>pred</sub> | 108.5 ± 5.2 | 9; 0.48 | 107.2 ± 3.9 | 10; 0.36 | 93.4 ± 4.7 | 8; 0.47 | 11.7 ± 6.3 | 10; 0.54 | 11.9 ± 5.7 | 11; 0.48 |
| EVLWI<sub>ad</sub> | 112.5 ± 5.4 | 10; 0.48 | 112.4 ± 4.1 | 11; 0.37 | 96.4 ± 4.6 | 7; 0.45 | 12.3 ± 6.4 | 10; 0.54 | 12.3 ± 5.9 | 11; 0.48 |
| EVLWI<sub>bc</sub> | 97.3 ± 4.2 | 9; 0.43 | 110.3 ± 3.8 | 11; 0.35 | 84.3 ± 3.8 | 7; 0.45 | 9.3 ± 4.3 | 8; 0.46 | 11.4 ± 5.5 | 10; 0.48 |
| EVLWI<sub>mat</sub> | 263.3 ± 11.9 | 242; 0.45 | 329.1 ± 11.7 | 314; 0.36 | 228.9 ± 11.7 | 210; 0.43 | 22.0 ± 10.4 | 20; 0.47 | 30.6 ± 13.3 | 28; 0.43 |
| P<sub>aw</sub> | 370 ± 155 | 329; 0.42 | 410 ± 140 | 400; 0.34 | 322 ± 132 | 283; 0.41 | 361 ± 171 | 298; 0.47 | 415 ± 178 | 372; 0.43 |
| P<sub>aw</sub>F<sub>O2</sub> | 4.20 ± 2.02 | 3.75; 0.48 | 4.19 ± 1.50 | 406; 0.36 | 360 ± 1.51 | 317; 0.42 | 4.6 ± 2.4 | 384; 0.57 | 452 ± 2.00 | 400; 0.44 |
| P<sub>aw</sub>F<sub>O2</sub> | 120.5 ± 56 | 102; 0.47 | 119; 43 | 111; 0.36 | 103 ± 47 | 88; 0.46 | 132 ± 69 | 113; 0.52 | 124 ± 62 | 110; 0.50 |
| P<sub>PaO2</sub> | 929 ± 20.7 | 900; 0.22 | 945 ± 20.1 | 916; 0.21 | 865 ± 16.7 | 833; 0.19 | 951 ± 22.1 | 960; 0.23 | 1211 ± 7.0 | 102; 0.58 |
| P<sub>FiO2</sub> | 0.47 ± 0.16 | 0.45; 0.34 | 0.44 ± 0.14 | 0.40; 0.32 | 0.51 ± 0.17 | 0.50; 0.33 | 0.46 ± 0.16 | 0.40; 0.35 | 59.6 ± 24.9 | 50; 0.42 |
| P<sub>PaO2/FiO2</sub> | 135 ± 4.4 | 130; 0.33 | 124 ± 3.4 | 120; 0.27 | 135.2 ± 4.4 | 130; 0.33 | 14.7 ± 5.1 | 130; 0.35 | 15.7 ± 4.3 | 15.6; 0.27 |
| P<sub>PaO2/FiO2</sub> | 219 ± 82 | 211; 0.37 | 230 ± 70 | 226; 0.30 | 182 ± 76 | 170; 0.42 | 188 ± 71 | 225; 0.38 | 242 ± 115 | 229; 0.48 |
| P<sub>PaO2/FiO2</sub> | 7.05 ± 5.95 | 5.9; 0.84 | 5.7 ± 3.5 | 5.0; 0.61 | 81.5 ± 5.9 | 70; 0.73 | 7.8 ± 7.5 | 60; 0.96 | 8.8 ± 6.4 | 6.8; 0.73 |
| PEEP | 6.8 ± 3.0 | 8.0; 0.35 | 7.9 ± 2.6 | 8.0; 0.33 | 8.9 ± 3.3 | 8.0; 0.37 | 9.1 ± 3.0 | 8.0; 0.33 | 8.8 ± 3.4 | 9.0; 0.39 |
| Measurements | 693 | 263 | 263 | 263 | 263 | 1426 |

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/Intra-group comparison \[ p < 0.001 \] vs. EVLWI<sub>ad</sub> for EVLWI<sub>ad</sub>, EVLWI<sub>bc</sub> and EVLWI<sub>mat</sub> within the same BMI-group.
/Inter-group comparison \[ p < 0.001 \] group with BMI < 30 kg/m² vs. group with normal BMI (BMI < 25 kg/m²).
/Inter-group comparison \[ p < 0.001 \] group with BMI ≥ 30 kg/m² vs. group with normal BMI (BMI < 25 kg/m²).
/\[ p > 0.05 \] group with BMI ≥ 30 kg/m² vs. group with normal BMI (BMI < 25 kg/m²).

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patients was markedly lower for EVLWI_{act} (0.41) than for EVLWI_{height} (0.57) or un-indexed EVLW (0.60). Inter-BMI-group-comparison demonstrated significantly lower values in patients with a BMI ≥ 30 kg/m² for EVLWI_{act}, EVLWI_{BMI}, EVLWI_{BSA} and EVLWI_{adj}, whereas there was no inter-group difference for EVLW, EVLWI_{pred}, EVLWI_{id}, EVLWI_{TLC}. In conclusion, significant inter-BMI-group-differences were found only for EVLWI_{act} and indexations including BW_{act} in their formulas (BW_{adj}, BMI and BSA) (Table 2).

2) Association of EVLWI(I) to parameters of pulmonary function. 2a.) Prediction of “PaO₂/FiO₂<200 mmHg” (primary endpoint) and “OI>10”: As demonstrated in Table 3, in the Munich-evaluation-group the greatest ROC-AUCs regarding “PaO₂/FiO₂<200 mmHg” were found for un-indexed EVLW (ROC-AUC 0.758; 95%-CI: 0.637–0.880) and EVLWI_{height} (ROC-AUC 0.746; 95%-CI: 0.622–0.869). EVLWI_{act} provided the lowest ROC-AUC (0.685, 95%-CI: 0.554–0.817).

In general, these observations were confirmed in the Antwerp-validation-group: EVLWI_{height} had the highest predictive capability (ROC-AUC 0.735; 95%-CI: 0.674–0.796), whereas weight-indexed EVLWI_{act} (ROC-AUC 0.710; 95%-CI: 0.648–0.773) and EVLWI_{BMI} (ROC-AUC 0.704; 95%-CI: 0.641–0.767) provided the smallest ROC-AUCs.

Statistical analysis of the merged data of both groups demonstrated a number of significant differences between different indexations, summarized as follows:

1) The greatest ROC-AUC regarding “PaO₂/FiO₂<200 mmHg” was found for EVLWI_{height} (ROC-AUC 0.729; 95%-CI: 0.674–0.784; primary endpoint).

2) The ROC-AUC was significantly greater for EVLWI_{height} compared to all other indexations including EVLWI_{act} (ROC-AUC 0.683; 95%-CI: 0.626–0.741; p = 0.007) and EVLWI_{pred} (ROC-AUC 0.707; 95%-CI: 0.630–0.763; p = 0.015).

Only un-indexed EVLW (ROC-AUC 0.728; 95%-CI: 0.673–0.783) and EVLWI_{BSA} (ROC-AUC 0.718; 95%-CI: 0.663–0.774; p = 0.137) were not significantly inferior compared to EVLWI_{height}.

Regarding the prediction of the threshold “OI>10”, in both collectives as well as in the merged data, the largest ROC-AUCs were obtained for EVLWI_{height} and EVLW, with the lowest for EVLWI_{act} (Table 4): 0.737 (0.589–0.885), 0.732 (0.583–0.881) and 0.669 (0.502–0.835) in the Munich-evaluation-group, 0.778 (0.713–0.842), 0.771 (0.705–0.836), and 0.739 (0.669–0.810) in the...
## Table 3: Comparison of receiver operating characteristics area under the curve (ROC-AUC) regarding "PaO2/FiO2 <0.200" and "Oxygenation-Index (OI) <10." depending on indexation of extravascular lung water (index) EVLW(I): ROC-AUCs for different indexations of EVLW(I) regarding "PaO2/FiO2 <0.200 mmHg" (left side of the table) and "OI <10"

| Patients | ROC-AUCs regarding "PaO2/FiO2 <0.200 mmHg" | ROC-AUCs regarding "OI <10." |
|----------|---------------------------------|-------------------|
| AUC      | p-values for comparison of ROC-AUCs | ROC-AUCs for different indexations of EVLW(I) regarding "PaO2/FiO2 <0.200 mmHg" (left side of the table) and "OI <10." |
| EVLW     | EWLWuset_EVLW          | EWLWuset_EVLW          | EWLWuset_EVLW          |
|          | EVLWuset_EVLW          | EWLWuset_EVLW          | EWLWuset_EVLW          |
|          | EVLWuset_EVLW          | EWLWuset_EVLW          | EWLWuset_EVLW          |
|          | EVLWuset_EVLW          | EWLWuset_EVLW          | EWLWuset_EVLW          |
|          | EVLWuset_EVLW          | EWLWuset_EVLW          | EWLWuset_EVLW          |
|          | EVLWuset_EVLW          | EWLWuset_EVLW          | EWLWuset_EVLW          |
|          | EVLWuset_EVLW          | EWLWuset_EVLW          | EWLWuset_EVLW          |
|          | EVLWuset_EVLW          | EWLWuset_EVLW          | EWLWuset_EVLW          |
|          | EVLWuset_EVLW          | EWLWuset_EVLW          | EWLWuset_EVLW          |
|          | EVLWuset_EVLW          | EWLWuset_EVLW          | EWLWuset_EVLW          |
|          | EVLWuset_EVLW          | EWLWuset_EVLW          | EWLWuset_EVLW          |
|          | EVLWuset_EVLW          | EWLWuset_EVLW          | EWLWuset_EVLW          |
|          | EVLWuset_EVLW          | EWLWuset_EVLW          | EWLWuset_EVLW          |
|          | EVLWuset_EVLW          | EWLWuset_EVLW          | EWLWuset_EVLW          |
|          | EVLWuset_EVLW          | EWLWuset_EVLW          | EWLWuset_EVLW          |
|          | EVLWuset_EVLW          | EWLWuset_EVLW          | EWLWuset_EVLW          |
|          | EVLWuset_EVLW          | EWLWuset_EVLW          | EWLWuset_EVLW          |
|          | EVLWuset_EVLW          | EWLWuset_EVLW          | EWLWuset_EVLW          |
|          | EVLWuset_EVLW          | EWLWuset_EVLW          | EWLWuset_EVLW          |
|          | EVLWuset_EVLW          | EWLWuset_EVLW          | EWLWuset_EVLW          |
|          | EVLWuset_EVLW          | EWLWuset_EVLW          | EWLWuset_EVLW          |
|          | EVLWuset_EVLW          | EWLWuset_EVLW          | EWLWuset_EVLW          |
|          | EVLWuset_EVLW          | EWLWuset_EVLW          | EWLWuset_EVLW          |
|          | EVLWuset_EVLW          | EWLWuset_EVLW          | EWLWuset_EVLW          |
|          | EVLWuset_EVLW          | EWLWuset_EVLW          | EWLWuset_EVLW          |
|          | EVLWuset_EVLW          | EWLWuset_EVLW          | EWLWuset_EVLW          |
|          | EVLWuset_EVLW          | EWLWuset_EVLW          | EWLWuset_EVLW          |
|          | EVLWuset_EVLW          | EWLWuset_EVLW          | EWLWuset_EVLW          |
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|          | EVLWuset_EVLW          | EWLWuset_EVLW          | EWLWuset_EVLW          |
| Group        | Parameter | Comparison to PaO₂/FiO₂ | Comparison to oxygenation index (mean airway pressure* FiO₂*/PaO₂) |
|--------------|-----------|--------------------------|------------------------------------------------------------------|
|              | r-value   | r²-value                 | r-value   | r²-value                 |
| Munich       | EVLW      | −0.34*                   | 0.12*     | −0.74**                   | 0.55**     | 0.44*     | 0.19**     | 0.80**     | 0.64**     |
| Munich       | EVLW_adj  | −0.21                    | 0.04      | −0.66**                   | 0.44**     | 0.32*     | 0.10**     | 0.57**     | 0.32**     |
| Munich       | EVLW_pred | −0.27                    | 0.07      | −0.69**                   | 0.48**     | 0.47*     | 0.22**     | 0.76**     | 0.58**     |
| Munich       | EVLW_deal | −0.26                    | 0.07      | −0.69**                   | 0.48**     | 0.48**    | 0.23**     | 0.76**     | 0.58**     |
| Munich       | EVLW_MSM  | −0.26                    | 0.07      | −0.72**                   | 0.52**     | 0.31*     | 0.10**     | 0.65**     | 0.42**     |
| Munich       | EVLW_BSA  | −0.28                    | 0.08      | −0.71**                   | 0.50**     | 0.42*     | 0.18**     | 0.71**     | 0.50**     |
| Munich       | EVLW.Height | −0.32*                | 0.10*     | −0.73**                   | 0.53**     | 0.45*     | 0.20**     | 0.78**     | 0.61**     |
| Antwerp      | EVLW      | −0.43**                  | 0.18**    | −0.68**                   | 0.46**     | 0.45*     | 0.20**     | 0.76**     | 0.58**     |
| Antwerp      | EVLW_adj  | −0.42**                  | 0.18**    | −0.63**                   | 0.40**     | 0.40**    | 0.16**     | 0.72**     | 0.52**     |
| Antwerp      | EVLW_pred | −0.43**                  | 0.18**    | −0.65**                   | 0.42**     | 0.44*     | 0.19**     | 0.73**     | 0.53**     |
| Antwerp      | EVLW_deal | −0.43**                  | 0.18**    | −0.65**                   | 0.42**     | 0.44*     | 0.19**     | 0.73**     | 0.53**     |
| Antwerp      | EVLW_BSA  | −0.38**                  | 0.14*     | −0.62**                   | 0.38**     | 0.37*     | 0.14**     | 0.70**     | 0.49**     |
| Antwerp      | EVLW.Height | −0.46**               | 0.21**    | −0.66**                   | 0.44**     | 0.46*     | 0.21**     | 0.75**     | 0.56**     |
| Antwerp      | EVLW.Height | −0.45**               | 0.20*     | −0.68**                   | 0.46**     | 0.47*     | 0.22**     | 0.76**     | 0.58**     |
| Munich       | EVLW      | −0.39**                  | 0.15*     | −0.68**                   | 0.46**     | 0.46*     | 0.21**     | 0.78**     | 0.61**     |
| Munich       | EVLW_adj  | −0.36**                  | 0.13*     | −0.60**                   | 0.36**     | 0.39*     | 0.15**     | 0.69**     | 0.48**     |
| Munich       | EVLW_pred | −0.38**                  | 0.14*     | −0.63**                   | 0.40**     | 0.46*     | 0.21**     | 0.75**     | 0.56**     |
| Munich       | EVLW_deal | −0.37**                  | 0.14*     | −0.60**                   | 0.36**     | 0.47*     | 0.22**     | 0.75**     | 0.56**     |
| Munich       | EVLW_BSA  | −0.38**                  | 0.14*     | −0.63**                   | 0.40**     | 0.44*     | 0.19**     | 0.71**     | 0.50**     |
| Munich       | EVLW.Height | −0.41**               | 0.17*     | −0.63**                   | 0.40**     | 0.42*     | 0.18**     | 0.72**     | 0.52**     |
| Antwerp      | EVLW.Height | −0.41**               | 0.17**    | −0.63**                   | 0.40**     | 0.42*     | 0.18**     | 0.72**     | 0.52**     |
| Antwerp      | EVLW.Height | −0.41**               | 0.17**    | −0.63**                   | 0.40**     | 0.42*     | 0.18**     | 0.72**     | 0.52**     |
| Antwerp      | EVLW.Height | −0.41**               | 0.17**    | −0.63**                   | 0.40**     | 0.42*     | 0.18**     | 0.72**     | 0.52**     |
| All Patients | EVLW      | −0.39**                  | 0.15*     | −0.68**                   | 0.46**     | 0.46*     | 0.21**     | 0.78**     | 0.61**     |
| All Patients | EVLW_adj  | −0.36**                  | 0.13*     | −0.60**                   | 0.36**     | 0.39*     | 0.15**     | 0.69**     | 0.48**     |
| All Patients | EVLW_pred | −0.38**                  | 0.14*     | −0.63**                   | 0.40**     | 0.46*     | 0.21**     | 0.75**     | 0.56**     |
| All Patients | EVLW_deal | −0.37**                  | 0.14*     | −0.60**                   | 0.36**     | 0.47*     | 0.22**     | 0.75**     | 0.56**     |
| All Patients | EVLW_BSA  | −0.38**                  | 0.14*     | −0.63**                   | 0.40**     | 0.44*     | 0.19**     | 0.71**     | 0.50**     |
| All Patients | EVLW.Height | −0.41**               | 0.17*     | −0.63**                   | 0.40**     | 0.42*     | 0.18**     | 0.72**     | 0.52**     |
| All Patients | EVLW.Height | −0.41**               | 0.17*     | −0.63**                   | 0.40**     | 0.42*     | 0.18**     | 0.72**     | 0.52**     |
| All Patients | EVLW.Height | −0.41**               | 0.17*     | −0.63**                   | 0.40**     | 0.42*     | 0.18**     | 0.72**     | 0.52**     |

Partial correlations were calculated with the individual patient as the controlling adjustment variable. *p<0.05  **p<0.001.
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provided high predictive capabilities compared to the first EVLW(AUC 0.603; 95%-CI: 0.424–0.782; p = 0.244).

**Discussion**

Data regarding EVLW-indexation are contradictory. Therefore, our study investigated the association between different indexations of EVLWI to PaO₂/FiO₂ and OI in two groups with mechanical ventilation and representative distribution of BMI. Our study demonstrated that

1. indexation of EVLWI to BWₐct is inferior to no indexation at all,
2. indexation to BWₚrd might provide a certain improvement compared to indexation to BWₐct and
3. indexation according to height or no indexation at all (EVLWI) are superior to indexation to BWₐct or BWₚrd.

These results are – at first glance – surprising, as several studies have suggested BWₚrd as the appropriate indexation factor [12–14].

Historically, different techniques have been established to quantify pulmonary edema termed as “EVLWI” which was originally determined without indexation. Early studies frequently used animal models with post-mortem gravimetric determination of EVLWI as the gold-standard [1, 2, 4, 10]. Regarding investigations in different species, indexation to BWₐct provided “basic” indexation allowing interspecies comparisons between different animal and human data.

However, in obese patients indexation to BWₐct might inappropriately diminish indexed EVLWIₚrd. Based on a better prediction of mortality rather than on a better correlation to PaO₂/FiO₂, superiority of EVLWIₚrd to EVLWIₚrd has been suggested: In the study by Phillips et al. [12] including 19 patients, EVLWIₚrd was not related to mortality. By contrast, mortality of the seven out of 19 patients was univariately associated to EVLWIₚrd. However, EVLWIₚrd obviously provided a better correlation to PaO₂/FiO₂ than EVLWIₚrd (coefficient of correlation: −0.525 for EVLWIₚrd and −0.773 for EVLWIₚrd). With only 19 patients included, this study did not approach a multivariate mortality-analysis. Another study that included 44 patients (225 measurements) demonstrated better discrimination of ARDS- and non-ARDS-patients by EVLWIₚrd compared to EVLWIₚrd [13]. A third study (44 patients; 44 measurements) showed the improved association of mortality by EVLWIₚrd compared to EVLWIₚrd in a multivariate model [14]. However, similarly to the data of Phillips et al. this study did not demonstrate a better correlation EVLWIₚrd to PaO₂/FiO₂ compared to EVLWIₚrd (coefficients of correlation −0.57 vs. −0.55). This is in accordance with two more recent studies suggesting a comparable [16] or even stronger [15] association of EVLWI compared to EVLWIₚrd with mortality.

Nevertheless, mortality is multifactorial, also depending on “do-not-resuscitate” statements and might be directly associated to some of the components of indexation (weight, BMI) [28-36]. E.g. further analysis of the data by Phillips et al. demonstrates that mean EVLWI and BMI were increased to a similar degree in the non-survivors compared to survivors (45% and 31%, respectively). Therefore, mortality is not an obvious endpoint to compare the appropriateness of different indexations of EVLWI, particularly when applied in small mono-centric collectives.

In our study-groups un-indexed EVLWI - next to EVLWIₚrd - provided the highest predictive capability regarding PaO₂/FiO₂ and OI. This indicates that particularly weight-based indexation
might be a confounder rather than an improvement of the inter-individual comparison of EVLW(I) in an adult population. In the analysis of patients' means, PaO2/FiO2 was significantly associated to unindexed EVLW, EVLW_I_height and EVLW_I_adj, whereas the correlation was not significant for all other indexations. These findings suggest that the association of EVLW(I) to PaO2/FiO2 might be obscured by inappropriate indexation. In general, the association of EVLW(I) was closer to OI compared to PaO2/FiO2. Including mean airway pressure in addition to PaO2/FiO2, OI also reflects the Positive End Expiratory Pressure (PEEP), peak and plateau pressure, ventilation mode (there is a usually higher mean airway pressure in controlled compared to assisted ventilation) as well as I:E ratio. Since the association of EVLW(I) to OI was not extensively investigated in the previous studies, the close association in our study might even strengthen the role of EVLW(I) as a parameter of pulmonary (patho)physiology.

With regard to indexation of other pulmonary parameters, the strong performance of height as an indexation for EVLW_I is not surprising. As stated in recent consensus guidelines “lung volumes are related to body size, with standing height being the most important factor” [21].

Furthermore, a look at the “weight correction-formulas” demonstrates that BW_pred and BW_id (Table 1) do not contain any weight at all, but simply adjust height for gender and subtract a length-constant [20, 21, 28].

In addition to weight and height, the third major determinant of most indexation formulas is gender, which has impact on BW_pred, BW_id, BW_adj and TLC. With regard to the above-mentioned formulas, indexation according to BW_id increases EVLW_I by 5.5% for women. EVLW_I_pred of women with a height between 150 and 190 cm is increased by 5–10% compared to men with the same height. However, this marked impact of gender on EVLW_I is not substantiated by our data: Multiple regression analysis regarding EVLW_I in our merged data including the variables age, height, weight, PaO2/FiO2 and gender demonstrated that gender was not independently associated to EVLW_I.

Finally, the question remains, whether in adults “no indexation at all” is the answer. Regarding our data in two adult groups with a high variability in body weight and BMI, but lower variability in

Figure 2. ROC curve regarding the prediction of mortality provided by first EVLW, last EVLW, APACHE-II and regression model combining first EVLW, last EVLW and APACHE-II.
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height, this might be a reasonable option. However, it must be kept in mind that the variability in height was low in these groups: e.g. mean height in the Munich-evaluation-group was 170 ± 10 cm (median 171 cm, range 150–190 cm).

On the other hand it is self-evident that indexation will improve the predictive capabilities in a group with a higher variability of parameters closely associated to EVLW such as height. There is elaborate data on the pulmonary function parameters in children and adolescents: Normal values in these groups with high variability in height and weight are mainly adjusted to height [20, 21].

Limitations of the study

Despite the inclusion of two different groups and the large sample size compared to the previous data, our study has several limitations. Our Munich-evaluation-group was a preselected group of non-operative mechanically ventilated patients with a prolonged ICU-stay. Although this drawback might be - at least in part - outweighed by a re-evaluation in a large group of non-selected anesthesiology patients, the data of both groups might not apply to patients without pulmonary impairment. On the other hand, the significance of modest correlations with r-values as low as -0.29 require cautious interpretation, since large numbers of patients promote significance of modest associations. Furthermore, these data are mainly derived from Caucasians. Despite a “considerable lack of data on lung-volumes in non-Caucasians” [20, 37] at least two studies give hints on differences regarding TLC between whites and blacks [38], Polynesians, Northern Indians and Pakistanis [39–41]. Finally, we cannot extrapolate our results to a pediatric population in which indexation to height may be much more appropriate than unindexed EVLW which was comparable to EVLWheight in our adult groups.

Conclusions

EVLW is a marker significantly associated to pulmonary function and mortality. Regarding the prediction of PaO2/FiO2 and OI, indexation of EVLWIheight is inappropriate. EVLWIred provides a slight improvement. The highest predictive capabilities in an adult population were found for EVLWIheight and unindexed EVLW. Therefore, our data suggest that EVLW should be indexed to height (EVLWIheight) or remain unindexed in adults.

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Author Contributions

Conceived and designed the experiments: WH JH TS CC MM RS. Performed the experiments: WH JH AU MF BS CC MM. Analyzed the data: WH JH TS BS CC MM RS. Contributed to the writing of the manuscript: WH JH TS BS CC MM RS.

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