

Utility of lung ultrasound for extravascular lung water volume estimation during cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

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ABSTRACT

Background and Aims: Rising extravascular lung-water index (ELWI) following cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS + HIPEC), if not timely intervened, can progress to pulmonary oedema. Transpulmonary thermodilution (TPTDL) is a standard technique to estimate ELWI (T-ELWI score), and track ongoing changes. Lung ultrasound (LUS) is another technique for ELWI (L-ELWI score) estimation. However, reproducibility and reliability of LUS for tracking serial L-ELWI changes during CRS + HIPEC remains to be validated. **Methods:** This prospective observational study included 360 L-ELWI and T-ELWI measurements at 12 peri-operative time-points. Cohen's Kappa test was used to assess reproducibility, Inter-rater agreement (between the anaesthetist and radiologist), and agreement between LUS and TPTDL for classifying the severity of pulmonary oedema. Reliability of LUS for 'tracking serial changes' in ELWI over time in individual patients was assessed by determining the repeated measures correlation (z-rrm) between weighted L-ELWI and T-ELWI scores. The ability of both techniques to discriminate pulmonary oedema was compared by analysing the area under ROC curves. **Results:** Excellent inter-rater agreement for assigned L-ELWI scores was observed (linear weighted $\kappa = 0.95$ for both). Both techniques had a good agreement in classifying the severity of pulmonary oedema (linear weighted $\kappa = 0.63$, 95% CI 0.51–0.79). T-ELWI and weighted L-ELWI scores correlated strongly (z-rrm = 0.88, 95% CI 0.80–0.92, $P < 0.0001$). Both techniques had comparable ability to discriminate pulmonary oedema (difference in area under ROC curve = 0.0014, 95%CI –0.0027 to 0.0055, $P = 0.5043$). **Conclusion:** We found the utility of LUS as a reliable and reproducible technique for ELWI estimation and tracking its changes over time in CRS + HIPEC.

Key words: Chest ultrasound, extravascular lung-water, hyperthermic intraperitoneal chemotherapy, pulmonary oedema, transpulmonary thermodilution

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INTRODUCTION

Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) are associated with release of pro-inflammatory mediators (PIMs) and often significant fluid shifts which can lead to fluid transudation into the lung interstitium measured as extravascular lung water index (ELWI).^[1,2] Normal ELWI levels are ≤ 10 ml/kg, however, values > 10 ml/kg are considered as fore-runners of pulmonary oedema and acute lung injury.^[3,4] Hence, early detection

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of rising ELWI facilitates pre-emptive measures to prevent - pulmonary oedema, the need for prolonged mechanical ventilation and hospital stay.^[1,4]

Ideally, ELWI estimation technique should be simple, portable, cost-effective, minimally invasive, reproducible, precise, and real-time. During CRS + HIPEC, single indicator transpulmonary thermodilution (TPTDL) is commonly used for objective quantification of ELWI (T-ELWI).^[3,5] However, it involves expensive equipment and disposables, central venous and femoral arterial (FA) cannulation, frequent calibration, controlled ventilation, and impedes patient's mobilisation; thus, confining widespread utility.

Lung ultrasound (LUS) provides a semi-quantitative ELWI score by counting the number of B-lines. It has advantages of being non-invasive, simple, portable, cost-effective, does not interfere with the patient's mobilisation, and has no risk of infection.^[6,7]

ELWI estimation by LUS (L-ELWI) has been evaluated in acute respiratory distress syndrome (ARDS), traumatic brain injury, chronic renal failure (CRF), and some post-surgical situations (cardiac and major vascular surgery), with good sensitivity and specificity.^[6-9] However, it is yet to be evaluated in CRS + HIPEC, which poses unique challenges due to potentially rapidly changing fluid kinetics. Further, concerns remain about the reproducibility and reliability of this operator-dependent technique.

Hence, we conducted this prospective study with the primary objective to evaluate the reproducibility and reliability of LUS by assessing its ability to classify patient's ELWI status, 'track serial changes' in ELWI scores over time, and inter-rater and test-retest reliability of L-ELWI measurements. The secondary objective was to evaluate the ability of LUS to discriminate the occurrence of pulmonary oedema.

METHODS

This prospective observational study was approved by the Institutional Review Board and all participants provided written informed consent. Fifty-two consecutive American Society of Anesthesiologists (ASA) physical status grade II-III, adult patients (age 20–75 years) having abdominal malignancy and peritoneal carcinomatosis requiring CRS + HIPEC were enrolled from October 2015 to December

2019. Patients with congestive heart failure, CRF, or contraindication for FA catheterisation were excluded. Patients with pre-operatively existing B-Lines due to conditions like pulmonary fibrosis, pneumonia, atelectasis, alveolar interstitial syndrome, and pleural effusion were also excluded. Thirty patients were finally statistically analysed; seventeen were excluded due to inoperability, four for technical fault in the Volumeview catheter or EV1000 clinical platform, and one due to refusal of consent.

General anaesthesia was given with muscle relaxation, inhalational agents, oro-tracheal intubation and epidural anaesthesia. T-ELWI values were obtained from Volumeview/EV 1000 clinical platform (V/EVCP, volumeview/EV 1000 clinical platform, Edwards Lifesciences, Irvine, CA, USA) after right internal jugular vein (IJV) and FA cannulation. T-ELWI can detect minimal fluctuation of 2 ml/kg fluid above normal in extravascular space of lung as rising ELWI values. T-ELWI score was graded as: ≤ 10 ml/kg – normal, $>10-13$ ml/kg - mild, $>13-15$ ml/kg - moderate, and >15 ml/kg – severe pulmonary oedema.^[3] Measured volumetric and haemodynamic parameters included - ELWI, pulmonary vascular permeability index (PVPI), global end-diastolic volume index (GEDVI), central venous pressure (CVP), stroke volume variation (SVV), cardiac index (CI), systemic vascular volume (SVR), heart rate (HR), and mean arterial pressure (MAP). Additionally, arterial blood gas (ABG), PaO₂/FiO₂, peripheral oxygen saturation (SpO₂), temperature, lactate, total fluid and blood transfused, and urine output were also recorded. Post CRS, HIPEC was performed for 90 minutes at 41-42°C by closed technique.

Intraoperatively goal-directed fluid therapy (GDT) was used. Crystalloids were transfused @ 2 ml/kg, and whenever required, additional 200 ml boluses of colloids were transfused to maintain SVV within the normal range (4-10). Norepinephrine infusion was titrated to keep MAP >65 mmHg to maintain CI >2.5 ml/kg/m². Blood was transfused if haemoglobin fell below 8 mg/dl. Post-operatively, GEDVI values (500-600 ml/m²) were targeted to maintain adequate preload, however, if T-ELWI values were >10 ml/kg, fluids were restricted.

During HIPEC, lung echogenicity changes due to the alveolar-interstitial interface thickening by high water content due to increased pulmonary capillary permeability and/or increased hydrostatic

pressure [HoP]. This creates B-Lines on LUS to provide L-ELWI score. LUS snapshots were captured in supine position (with arms by the side) by using a multi-frequency 6-13 MHz linear array transducer (Micromaxx™ Ultrasound system; Sonosite Inc. Bothell, WA, USA). The transducer probe was placed longitudinally in the midclavicular line over the 2nd-4th intercostal space (ICS), and the anterior axillary line over the 3rd-5th ICS on both sides of the chest. Right, and left-sided chest scanning areas were labelled as 1–2 and 3–4, respectively. Absence (0 B-line score) or presence of single or confluent B-Lines (from all four scanning areas) were finally summed-up to derive a semi-quantitative L-ELWI score [Table 1].^[8] Unlike the TPD L technique, LUS cannot quantify the absolute amount of water in the lung. The L-ELWI score was graded as follows: ≤6 - normal, 7-15 - mild, 16-30 - moderate, and >30 - severe pulmonary oedema.^[9] Two anaesthetists (experience of >500 LUS scans) captured all LUS snapshots which were re-evaluated by an experienced radiologist (having experience of >10 years of lung scanning and blinded to the anaesthetist's findings) to assess the inter-rater agreement of assigned L-ELWI scores (anaesthetist versus radiologist). A week apart, snapshots were reassessed (same radiologist) to re-assign L-ELWI scores to evaluate the test-retest reliability of the LUS technique.

T-ELWI scores (after calibration of V/EVCP) and L-ELWI score were obtained at the following time points - T0: After induction, T1: After completion of CRS and before HIPEC, T2-T4: Every 30 minutes starting 30 minutes after beginning HIPEC, T5: After completion of CRS and HIPEC, T6–T12: Postoperative readings taken at a gap of every 12 hours till the third postoperative day (POD). At each time point, L-ELWI scores were obtained by the anaesthetist (not involved in patient management), and later after a gap of five

minutes, T-ELWI scores were obtained by second anaesthetist blinded to L-ELWI values. Pulmonary oedema was clinically evaluated peri-operatively by monitoring SpO₂ (SpO₂ <90%), coarse crepitations on auscultation, and pink frothy pulmonary secretions. Besides these, a chest radiogram was requested post-operatively for identification of Kerley B-lines and opacities.

Continuous and count data were described as mean [standard deviation (SD)] and numbers (proportion), respectively. Cohen's weighted kappa with linear weights was used to assess - inter-rater (radiologist and anaesthetist) and test-retest agreement of assigned LUS scores. It was also used to assess the agreement between LUS and TPTDL techniques in classifying patients as having no, mild, moderate or severe pulmonary oedema. Relative validity L-ELWI measurements for 'tracking serial changes' in ELWI scores over time in individual patients was assessed by determining their correlation with T-ELWI values. Assessing correlation by conventional statistical tests assumes independence of error between observations which is violated when repeated observations are obtained from the same individuals. 'Repeated measures correlation' (rmcorr) was used to analyse covariance to statistically adjust for intra-individual variability, thus accounting for non-independence among observation pairs.^[10]

Rmcorr coefficient (rrm) is bounded by -1 to 1 and represents the strength of the linear association between two variables. Since TPTDL and L-ELWI have different scales, we standardised L-ELWI scores by obtaining the difference between the observed value (Xi) and the baseline value (X0) for every subject, and these weighted scores were used for analysing correlation (z-rrm). Receiver operating characteristic curves (ROC) were analysed to compare L-ELWI and T-ELWI [by assessing area under the curve (AUC)] in their ability to discriminate clinical pulmonary oedema. All statistical tests were two-tailed, and alpha <0.05 was set as significant before-hand. Descriptive statistics, ROC and kappa statistic, were analysed using MedCalc (version 15.8). Longitudinal secular trends of T-ELWI and repeated measures correlation were analysed and drawn using R program (v3.6.1) utilising following packages: 'ggplot2', 'ggpubr', 'dplyr' and 'rmcorr'. All ELWI measurements for analysis refer to those measured by the TPTDL method unless mentioned otherwise. All L-ELWI measurements used for analysis refer to those scored by the radiologist

Table 1: Criterion for ultrasound extravascular lung water index (L-ELWI) score computation by identifying and calculating the B-lines in assigned intercostal spaces (ICs)

Ultrasound findings	Score
No B-Lines/ICS	0
One B-Lines/ICS	1
Two B-Lines/ICS	2
Three B-Lines/ICS	3
Four B-Lines/ICS	4
Five B-Lines/ICS	5
Confluent B-Lines >50% ICS	6
Confluent B-Lines >75% ICS	7
Confluent B-Lines >100% ICS	8

unless mentioned otherwise. The sample size was estimated based on the findings of the study by Anile *et al.*^[6] who reported a significant correlation between the number of lung quadrants positive for B-lines and ELWI index using predicted body weight ($\rho = 0.493$). Thus, 30 patients were required to have an 80% chance of detecting the same magnitude of correlation as significant with type one error set at 5%. Although we ultimately chose 'rmcorr' (and not conventional ρ), repeated measures design only raises the power of the study further by increasing the number of observations.

RESULTS

Thirty patients comprised the study cohort. Tables 2 and 3 describe their demographic, clinical and surgical details. Total 360 measurements were performed to obtain T-ELWI and L-ELWI scores at 12 different time points. Intra-operatively, ELWI scores stayed within the normal range, while rising ELWI scores were noted only postoperatively [Figure 1].

While assigning L-ELWI scores, very good inter-rater agreement (linear weighted $\kappa = 0.95$, SE = 0.007, 95% CI = 0.94–0.97), and very good test-retest reliability (linear weighted $\kappa = 0.95$, SE = 0.006, 95% CI = 0.94–0.96) were noted.

Similarly, very good agreement between both techniques for classifying normal from the abnormal ELWI scores was found (linear weighted $\kappa = 0.88$, SE

0.04, 95% CI = 0.79–0.96). A good agreement between L-ELWI and T-ELWI was noted while categorising the ELWI grades as normal, mild, moderate or severe pulmonary oedema (Linear weighted $\kappa = 0.63$, SE 0.05, 95% CI = 0.51–0.74).

L-ELWI scores were found to strongly correlate with T-ELWI scores while 'tracking serial changes' in ELWI scores over time ($z\text{-rrm} = 0.88$, 95% CI 0.80–0.92, $P < 0.0001$), [Table 4]. Pulmonary oedema was noted in 7 readings, and was identified by both LUS

Table 2: Demographic, systemic co-morbidities and details of malignancy of all participants that underwent CRS + HIPEC

Variables	Values
Demographic Variables	
Age in years, mean (\pm SD)	48.1 (\pm 12.3)
Gender, male, females, n (%)	10 (33.3%), 20 (67%)
Weight (kg), mean (\pm SD)	63.03 (\pm 11.3)
Body Mass index (kg/m^2), mean, (\pm SD)	24.30 (\pm 3.80)
PCI, mean (\pm SD)	9.96 (\pm 2.91)
*Pre-operative comorbidities, n (%)	9 (30)
Cardiovascular, n (%)	5 (16.67)
Pulmonary, n (%)	2 (6.7)
Neurological, n (%)	1 (3.33)
Endocrine, n (%)	5 (16.67)
Obesity (BMI >35), n (%)	2 (6.7)
Primary source of malignancy	
Ovary, n (%)	14 (46.67%)
Colorectal	7 (23.33%)
Appendix	6 (20%)
Gastric	3 (10%)

*Few patients had more than one co-morbidities. SD-Standard deviation; BMI-Body mass index; PCI-Peritoneal cancer index

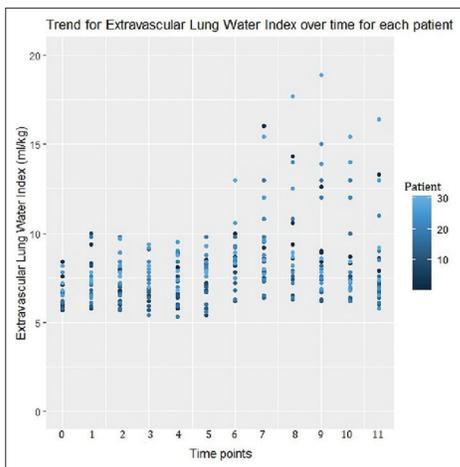


Figure 1: Trend of extravascular lung water index (ELWI) at all peri-operative time points (T0-T11) for each patient. #Extravascular lung water index values were obtained by the transpulmonary thermodilution technique. Intraoperative time points: T0-T5, Postoperative time points: T6- T11. *ELWI >10 ml/kg, is considered as cut-off value for clinical pulmonary oedema to be present, few patients had higher ELWI score in postoperative period. §Mean ELWI value of each participant is displayed in the colour with different intensity

Table 3: Intraoperative fluid intake/output details, postoperative complications and modality used for the management of respiratory distress in the participants that underwent cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC)

Intraoperative intake/output details	Mean, (\pm SD)
Duration of CRS+HIPEC, min	390.87 (\pm 98.87)
Intraoperative intake of fluid, mean, (\pm SD) ml	8373.1 (\pm 2635.3)
Intake of fluid in ml/kg/h	16.44 (\pm 3.96)
Blood loss, mean, (\pm SD) ml	823.7 (\pm 699.7)
Urine output, mean, (\pm SD) ml	592.63 (\pm 293.49)
Post-operative complications, n (%)	9 (30)
Total Pulmonary complications, n (%)	7 (23.33)
Postoperative Pulmonary oedema, n (%)	2 (6.67),
Atelectasis, Pleural effusion, n (%)	4 (13.3), 2 (6.7)
Cardiovascular, n (%)	1 (3.3)
Renal, n (%)	1 (3.3)
Respiratory distress management details, n (%)	7 (23.33)
Post-operative ventilator support, n (%)	1 (3.3)
BIPAP, n (%)	2 (6.7)
HFNC, n (%)	4 (13.3)

HFNC: High flow nasal cannula, BIPAP: Bilevel positive airway pressure, SD: Standard deviation

Table 4: Association of extravascular lung water scores derived from transpulmonary thermodilution technique with other volumetric and pulmonary parameters

Variables	Correlation coefficient (r_{rm}), 95% CI, P
T-ELWI and L-ELWI	0.88, 0.80-0.92, <0.00001
T-ELWI and PVPI	0.45, 0.36-0.53, <0.0001
L- ELWI and PVPI	0.31, 0.21-0.40, <0.0001
T- ELWI and GEDVI	0.53, 0.45-0.60, <0.00001
T- ELWI and CVP	0.23, 0.13-0.33, <0.0001
T- ELWI and PaO ₂	-0.20, -0.30 to -0.09, 0.0002
L- ELWI and PaO ₂	-0.21, -0.31 to -0.11, <0.0001
T- ELWI and Lactate levels	0.27, 0.17-0.37, <0.0001
T- ELWI and SVV [#]	-0.12, -0.27 to 0.04, 0.13
T-ELWI and CI [#]	0.01, -0.15 to 0.16, 0.91
T- ELWI and Temperature	-0.01, -0.10 to 0.10, 0.99
T- ELWI and SVR	0.06, -0.05-0.17, 0.28

T-ELWI: Transpulmonary thermodilution extravascular lung water index, L-ELWI: Ultrasound extravascular lung water index, PVPI: Pulmonary Vascular Permeability Index; GEDVI: Global End-diastolic Volume; CVP: Central Venous Pressure; SVR: Systemic Vascular Resistance. SVV: Stroke Volume Variation; CI: Injectate cardiac output. [#]Repeated measures correlation between ELWI and other parameters included all peri-operative (T0-T11) time points however for CI and SVV includes only intraoperative time points (T0-T5)

and TPTDL techniques. Both T-ELWI and L-ELWI demonstrated excellent ability for discriminating pulmonary edema [AUC 1.0 (95% CI - 0.989 to 1.00, $P < 0.0001$) and 0.998 (95% CI -0.986 to 1.00, $P < 0.0001$), respectively]. The difference in the area under curves was statistically insignificant (0.0014, 95%CI = 0.0027–0.0055, $P = 0.50$).

Perioperatively, T-ELWI values were found to significantly correlate with PVPI, GEDVI, CVP, Pao₂/FiO₂ and lactate levels [Table 4]. However, it did not significantly correlate with SVV, CI, SVR, and temperature.

DISCUSSION

The postoperative phase after CRS + HIPEC is critical, and at risk for rising ELWI values, that may affect oxygenation index, duration of mechanical ventilation, length of intensive care unit (ICU) stay, and mortality.^[1,2,11-14] LUS is gaining popularity as a reasonably accurate tool for the detection of pulmonary interstitial oedema with high sensitivity and specificity.^[6-9] ELWI has been estimated only by TPTDL technique during CRS + HIPEC, and authentication of LUS technique to identify and grade the severity of ELWI scores and track its serial changes with time is lacking.^[3]

Observer dependence is often lamented as the Achilles heel of any ultrasonographic assessment. We found

very good agreement between LUS observations of two independent assessors (linear weighted $\kappa = 0.95$). A similar good inter-rater agreement has been reported by others in different clinical situations.^[7,8] Furthermore, we also assessed for test-retest reliability and found excellent agreement (linear weighted $\kappa = 0.95$).

Different scales of measurements of T-ELWI and L-ELWI preclude direct comparison due to statistical limitations. However, we found very good agreement between both techniques for differentiating normal from abnormal ELWI scores (Cohen's Kappa 0.88). Similarly, good agreement between these techniques was noted for grading the ELWI scores as normal, mild, moderate or severe pulmonary oedema (Kappa 0.63). It can be argued that the clinical status of the patient is more relevant to the clinician in lieu of absolute ELWI values, to make decisions. Observed strong correlation ($z_{rrm} = 0.88$) between L-ELWI and T-ELWI scores attests to the relative validity L-ELWI measurements for 'tracking serial changes' in ELWI values over time. Others have reported similar or lower correlation coefficients (0.40-0.91). However, our statistical technique of repeated measures correlation using weighted scores is more robust and has not been used in relevant literature so far.^[6-9] Moreover, this variation in reported correlation coefficients could be due to disparity in the area and the number of ICSs scanned lung scanning protocols and assessor's proficiency.

L-ELWI technique correctly identified all seven instances of clinical pulmonary oedema. The excellent area under the ROC curve with an insignificant difference between the AUC of T-ELWI and L-ELWI for discriminating clinical pulmonary oedema further endorses its diagnostic utility. Enghard *et al.*^[8] reported the similar diagnostic potential of the LUS technique for ELWI evaluation, categorisation of the severity of raised ELWI scores and for tracking the serial changes in ELWI over time in an individual. Altogether these findings, make a strong case for the utility of the LUS technique in L-ELWI computation.

Postoperatively, PVPI values significantly correlated with T-ELWI levels ($r_{rm} = 0.45$, Table 4). Six hours after CRS or HIPEC, levels of PIMs start intensifying and peak by 12 hours, and fade over the next 24-48 hours.^[4,15-18] Increasing PIMs are mainly responsible for endothelial barrier disruption in interstitial or vascular tissue, leading to extensive leakage not only in the tumour microenvironment but also in the systemic and pulmonary vasculature.^[4,19,20]

Rising ELWI scores due to increased HoP have been observed during cardiogenic pulmonary oedema, Chronic renal failure (CRF), Acute respiratory distress syndrome (ARDS), and other critically ill patients.^[4-9,11,12] We found a moderate correlation of GEDVI (rrm = 0.53) with T-ELWI, indicating the impact of HoP on ELWI. The influence of HoP can be minimised by limiting intraoperative fluid transfusion up to 20 ml/kg/hr or by opting GDT guided transfusion.^[1,2,13,21] Hasanin *et al.*^[22] advocated GDT to lower ELWI, which improves PaO₂/FiO₂ and lung oxygenation. We also found an inverse and weak association between PaO₂/FiO₂ and ELWI (rrm 0.20, Table 4). Thus, serial ELWI tracking could help to improve lung oxygenation and minimise postoperative pulmonary complications.

Limitation of the study is that for ELWI computation, LUS scanning should ideally be performed in 28 ICSs for robust B-lines computation. However intraoperatively, due to the presence of surgical screens, drapes, and the patient's both arms by the side, only anterior and lateral ICS were scanned. Post-operatively, extended field ICS scanning was limited by the patient's restricted movement (pain and discomfort). However, we do not see it as a limitation, but rather the only way by which LUS can be practically performed in such a scenario. Furthermore, post-operatively B-lines could be found in conditions like lung atelectasis, collapse and pneumonia. Hence, falsely higher ELWI scores are possible. Moreover, compared to TPTDL, LUS cannot differentiate the aetiology for raised ELWI scores. Our patients had low Peritoneal Cancer Index (PCI) scores (likely to have less PIMs and fluid shifts), and evaluation of this technique in patients with higher PCI remains to be seen, though experience from other surgeries (such as major cardiac and vascular surgeries) indicates that the LUS technique may hold good.

CONCLUSION

We found utility of non-invasive LUS as a reliable and reproducible technique for the estimation, categorisation and tracking serial changes in ELWI over time during CRS + HIPEC. Moreover, it has a good discriminative ability for the detection of clinical pulmonary oedema.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to

be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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