A Nomogram to Predict the Potential Risk of Encapsulating Peritoneal Sclerosis in Patients Receiving Peritoneal Dialysis

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Introduction and Objectives

- **Introduction**
  Encapsulating peritoneal sclerosis (EPS) is a rare but serious complication of peritoneal dialysis (PD). It is characterized as a gross thickening of the peritoneum enclosing the small intestine in a cocoon of opaque tissue. The most important risk factor for EPS is the duration of PD. EPS is often associated with high mortality due to late diagnosis. Matrix metalloproteinase 2 (MMP2) is a protein that is involved in the breakdown of extracellular matrix. Recently, the use of effluent MMP-2 level as a potential biomarker of peritoneal fibrosis and EPS have been demonstrated in PD patients. Since there is no good clinical tool to estimate the risk of EPS, we attempted to develop a nomogram to fill in this gap.
- **Objective**
  To develop a nomogram based on effluent MMP-2 level and clinical parameter to predict EPS in PD patients

Methods

- **Study population and design**
  Eighteen EPS patients and 90 PD patients from 3 tertiary hospitals of Taiwan were enrolled in this study, using a 1:5 cross-sectional, case-control design. EPS cases were identified by 2 experienced nephrologists and a radiologist based on predefined criteria. Patients who did not develop EPS were selected randomly from the same base population as controls. Ninety percent of control patients had PD duration for more than 5 years. All patients were free from peritonitis in preceding one month before effluent collection. Demographic characteristics and clinical data such as age, sex, primary kidney disease, PD duration, number of peritonitis episodes, and blood biochemistry were documented. The Ethics Committee of the three hospitals approved this study protocol, and informed consents were obtained from all patients.
- **Specimen collection and biochemical assays**
  The overnight peritoneal effluents were collected from all patients during a period of April through September 2016. The effluent were sent to a central laboratory for measurement of MMP-2. The effluent MMP2 levels were measured using the Human MMP-2 ELISA Kit (Catalog Number KHC3081) from Invitrogen. The MMP-2 levels were standardized for per mg/dl of total protein in the effluent. None of the dialysate MMP-2 levels were below the detection limit. There were no missing data. The number of episodes of peritonitis were recorded based on the review of medical records.
- **Statistical analysis**
  Data are reported as the mean (standard deviation), median [interquartile range, IRQ], or frequency (percentage), as appropriate. All continuous variables were tested for normality using the skewedness and kurtosis test. Data was analyzed using the *t*-test for normally distributed variables, the Mann-Whitney U test for non-normalized variables, or the chi-squared test for categorical variable. Possible factors associated with EPS were analyzed using univariate logistic regression, followed by multivariate logistic regression. Factors that are significantly associated with EPS in multivariate logistic regression were selected for the constitution of the nomogram for EPS. The accuracy of the nomogram was estimated using by the area under the receiver operating characteristic curve (AUC).

All analyses were performed using pROC packages of R Statistical Software (version 3.3.2, R Foundation for Statistical Computing, Vienna, Austria). Values with $p < 0.05$ were considered as statistically significant.

Results

- **Study population**
  The clinical characteristics were shown in Table 1. The median age was younger in EPS group than controls (52 vs. 58 years of control group, p<0.032), while the median PD duration of EPS group was significantly longer when compared to control group (13 vs. 8 years, p<0.001).
- **Analysis of MMP-2 in the peritoneal effluent**
  The peritoneal effluent MMP2 levels (median 87.36, interquartile range 5.67 - 179.77 ng/mg) of EPS patients were significantly higher than that of control patients (16.81, 2.32 - 54.01) (p < 0.001, Manny-Whitney U test) (Fig.1). Univariate analysis revealed effluent MMP2 and PD duration were independently associated with EPS risks (p < 0.001 and p = 0.001) (Table 2). The odds ratio (OR) was 74.70 [95% confidence interval (CI): 7.36-758.00] in per log unit of MMP-2 increase and was 1.28 (95% CI: 1.03-1.60) for one additional year of PD duration.
- **Nomogram to predict potential risk of EPS**
  A nomogram based on MMP-2 and PD duration was proposed (Figure 2). The AUC of MMP2 was 0.824 for the prediction of EPS and the accuracy of the prediction was further improved by adding the duration of PD (p = 0.05). The AUC of the nomogram was 0.907 for the prediction of EPS. For example, the effluent MMP-2 level of 90 ng/mg gained 5 points, an 18-years PD duration gained 3.5 points, and putting together with a total point of 8.5, suggesting a potential EPS risk of 0.98.

Dicussions

- The findings of this study support that effluent MMP-2 level may be useful in the prediction of EPS in chronic PD patients. The addition of PD duration may further improve the accuracy of the prediction of EPS.
- The increased MMP-2 level in the PD effluent in EPS may be the result of breakdown of vascular basement membrane by MMP2, as the breakdown of vascular basement membrane is the first step to induce neovascularization. The neovascularization is associated with increased solute transport in the peritoneum membrane and MMP-2 levels are positively associated with increased solute transport in the peritoneum in animal models of EPS.
- The PD duration is the other component of the nomogram. It is well recognized that longer PD duration is related to increased risk of EPS
- The standardization of MMP2 level by using total effluent protein level is critical because the solute transport may be changed in EPS as well as other chronic inflammation or infection in the peritoneum. The change of solute transport may increase the total protein levels in the effluents and some of the proteins measured in the effluent may not be specific to EPS.

Limitations

- The number of EPS patients are limited in this study due to rarity of EPS. A larger cohorts of PD related- EPS patients are needed to validate the accuracy of this study.
- Some information of unknown factors that may be associated with the EPS may not be collected in this study.

Conclusions

- Higher effluent MMP2 level is associated with an increased risk of EPS in chronic PD patients. The predictive accuracy of EPS can be further improved using the nomogram that consists of effluent MMP2 levels and PD duration.
- The nomogram may provide a simple tool in identifying PD patients who are at risk of developing EPS. A larger cohort to verify our nomogram is mandatory in the future.

Table 1. Clinical characteristics of patients

Factor	Control	EPS	p
n	90	18	
Male sex (%)	39 (43.3)	6 (33.3)	0.602
Age (year)	59 (11)	52 (13)	0.032
PD duration (year)	8 [1, 19]	13 [6, 20]	<0.001
Albumin (g/dl)	3.61 (0.36)	3.53 (0.54)	0.478
Calcium (mg/dl)	9.50 (0.81)	9.54 (0.84)	0.871
Creatinine (mg/dl)	11.41 (2.82)	8.74 (2.61)	0.017
Phosphorus (mg/dl)	4.99 (1.27)	4.34 (1.32)	0.052
MMP-2 (ng/mg)	16.81 [2.32, 54.01]	87.36 [5.67, 179.77]	<0.001
Peritonitis episodes(n)	1 [0, 6]	1 [0, 7]	0.12

EPS: encapsulating peritoneal sclerosis, MMP-2: matrix metalloproteinase-2
Albumin, Creatinine, Calcium. Phosphorus: Serum levels of solutes

Table 2. Odds ratios (ORs) of possible risk factors for EPS

Factor	Univariate analysis	Multivariate analysis
	OR (95% CI)	OR (95% CI)
MMP- 2*	156 (18.10-1350)	74.70 (7.36-758.00)
Age	0.95 (0.91-1.00)	0.96 (0.89-1.03)
PD duration	1.38 (1.18-1.61)	1.28 (1.03-1.60)
Phosphorus	0.64 (0.41-1.02)	-
Albumin	0.63 (0.18-2.24)	-
Calcium	1.05 (0.56-1.98)	-
Creatinine	0.62 (0.41-1.03)	-
Peritonitis	1.32 (0.97-1.80)	-

*log transform, MMP-2: matrix metalloproteinase-2

Fig 1. MMP2 effluent levels are much higher in EPS than controls (p<0.001)

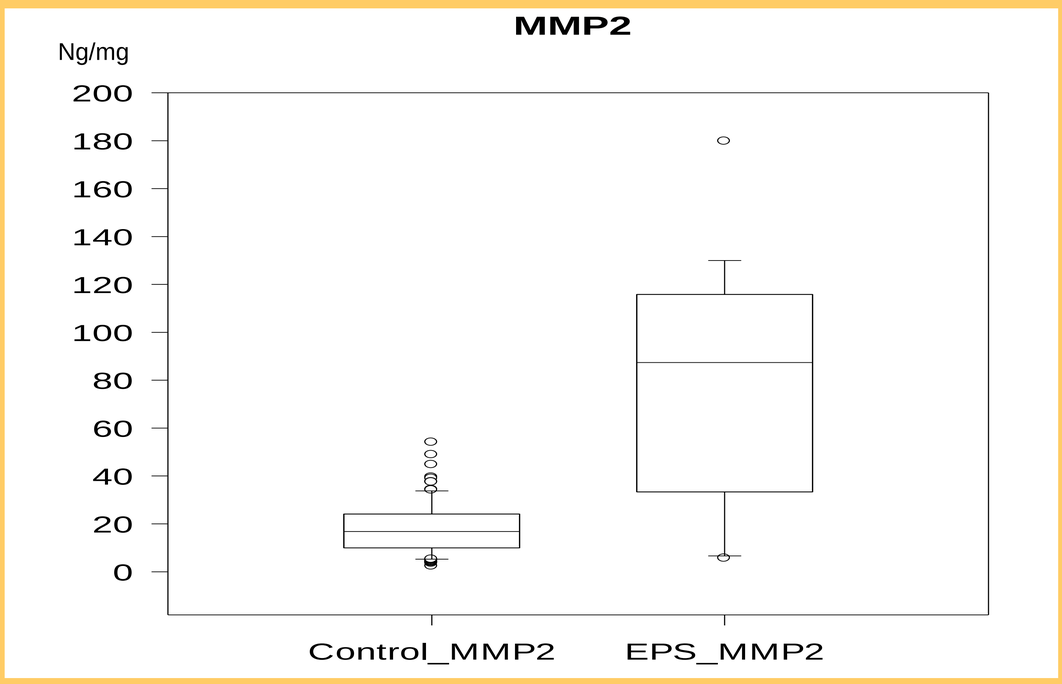
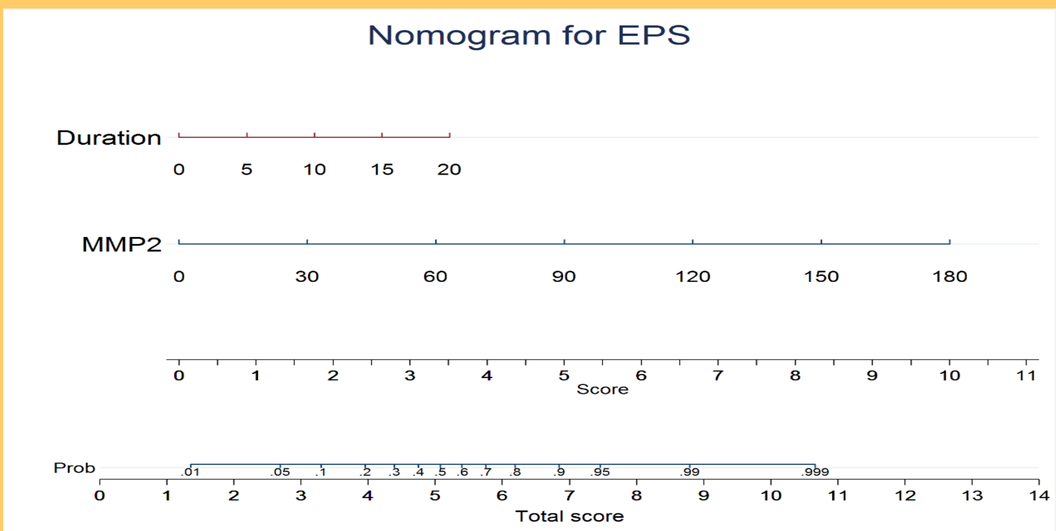


Fig 2. Nomogram to predict the risk of EPS in PD patients



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