AABIP JOURNAL CLUB

DEVELOPMENT AND VALIDATION OF RESPONSE MARKERS TO PREDICT SURVIVAL AND PLEURODESIS SUCCESS IN PATIENTS WITH MALIGNANT PLEURAL EFFUSION (PROMISE): A MULTICOHORT ANALYSIS

THE CLINICAL QUESTION

Can a survival score for malignant pleural effusion (MPE) be developed using a combination of conventional and pleural fluid-based biomarkers and be validated on prospective data?

TAKE HOME MESSAGE

The clinical PROMISE score (comprising hemoglobin, serum CRP, serum WBC, ECOG score, type of cancer, and history of chemotherapy or radiotherapy) can accurately predict mortality at 3 months among patients with MPE (c-statistic 0·89 [95% CI 0·84–0·93]).

Although the incorporation of pleural TIMP1 levels did not result in an appreciable improvement in model performance, the biological discovery component of this study sheds useful light on novel biological pathways with the potential to guide new treatments of MPE.

BACKGROUND

- MPE is associated with a highly variable prognosis, ranging anywhere from several days to over a year.
- Accurate prognostication is important for patient counseling as well as choice of management. For example, the relative cost-effectiveness of pleurodesis versus tunneled pleural catheter placement may vary with life expectancy.
- The LENT score, developed on pre-existing study cohorts, offers an estimate of median survival, but has not been validated on prospective data.
- Clinicians and clinical trial investigators continue to struggle in terms of accurately prognosticating MPE patients, especially those with very low survival.

STUDY DESIGN

Multi-phase study comprising the following:
(1) Biological biomarker discovery (using mass spectrometry), clinical biomarker discovery, and model development using retrospective data and pleural fluid samples from the TIME1, TIME2, and TIME3 study cohorts (n = 502);
(2) Prospective external validation on the SIMPLE study and the Oxford Radcliffe Pleural Biobank (n = 162)
Primary outcome: Mortality at 3 months

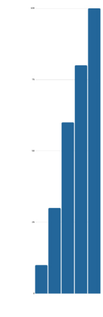
POPULATION

Inclusion criteria
- Patients with MPE who were at least 18 years old

Exclusion criteria
- Expected survival less than 1 month

Baseline Characteristics
Baseline characteristics of the TIME1 (n = 320), TIME2 (n = 106), and TIME3 (n = 126) cohorts have been published previously. Mean age was around 70 years in all cohorts.

OUTCOMES



A total of 25 candidate biomarkers were tested for prediction of 3-month survival. These included demographics (age and sex), cancer type, history of chemotherapy or radiotherapy, illness severity, serum laboratory values, and pleural fluid proteins. The clinical PROMISE score included the following seven biomarkers: Serum hemoglobin, serum CRP, serum WBC, ECOG score, type of cancer, history of chemotherapy, and history of radiotherapy.

Primary outcome
The clinical PROMISE score accurately predicted 3-month mortality among patients with MPE (C statistic 0·89 [95% CI 0·84–0·93]). While pleural fluid TIMP-1 was also predictive of survival, adding it to the clinical score (to form the biological PROMISE score) did not appreciably improve prognostic performance (C statistic 0·90 [95% CI 0·84–0·93]).The corresponding C statistic for the previously published LENT score was 0·75 [95% CI 0·68–0·81].(Note: The C statistic (also called concordance statistic) is equivalent to the area under a Receiver Operating Characteristic (ROC) curve and quantifies the predictive performance of a logistic regression model, with values >0.8 generally indicating a strong model)

COMMENTARY

A major strength of the study is external validation on prospective data. However, a major limitation is that it excluded patients with survival less than 1 month and furthermore, only predicted risk of mortality at 3 months as opposed to the specific life expectancy for a given patient. For these reasons, the PROMISE score offers no assistance in identifying patients with very low survival (1 month or less), which as mentioned in the 2018 ATS/STS/STR guidelines remains a considerable challenge for clinicians and study investigators alike.

A notable strength from the perspective of advancing our understanding of disease is that the study identified novel biologic pathways through a proteomics-based discovery phase with the potential to guide new treatments of MPE.

FUNDING

European Respiratory Society, Medical Research Funding-University of Oxford, Slater & Gordon Research Fund, and Oxfordshire Health Services Research Committee Research Grants

SUGGESTED READING

1. Clive AO, Kahan BC, Hooper CE, et al. Predicting survival in malignant pleural effusion: development and validation of the LENT prognostic score. Thorax. 2014;69(12):1098-1104.
2. Psallidas I, Kannelakis N, Yousuf A, et al. LENT score validation on patients with malignant pleural effusion. European Respiratory Journal. 2016;48(suppl 60):PA338.
3. Feller-Kopman DJ, Reddy CB, DeCamp MM, et al. Management of Malignant Pleural Effusions. An Official ATS/STS/STR Clinical Practice Guideline. Am J Respir Crit Care Med. 2018 Oct 1;198(7):839-849.

ARTICLE CITATION

Psallidas I, Kanellakis NI, Gerry S, Thézénas ML, Charles PD, Samsonova A, Schiller HB, Fischer R, Asciak R, Hallifax RJ, Mercer R, Dobson M, Dong T, Pavord ID, Collins GS, Kessler BM, Pass HI, Maskell N, Stathopoulos GT, Rahman NM. Development and validation of response markers to predict survival and pleurodesis success in patients with malignant pleural effusion (PROMISE): a multicohort analysis. Lancet Oncol. 2018 Jul;19(7):930-939.

If you would like to become a reviewer for the "**AABIP Journal Club**," Please contact **Christian Ghattas** at **christian.ghattas@osumc.edu**