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The International Normalized Ratio of Prothrombin Time in the MELD Score: A Reliable Measure

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Abstract

The Model for End-stage Liver Disease has been demonstrated to be an excellent predictor of survival in patients with end-stage liver disease. It is derived from the International Normalized Ratio (INR) of prothrombin time, serum creatinine, and serum total bilirubin. The major use of the MELD score is to prioritize allocation of organs for liver transplantation among patients with chronic liver disease. The INR may be incorrect in liver disease because of generic factors, and factors specific to liver disease. In spite of these limitations, virtually every study that has looked at the MELD score as a predictor of survival has demonstrated that the MELD score using the INR with ISI calibrated for patients on warfarin has a 'c' statistic of approximately 0.8, indicating excellent discrimination. Thus, although the current method of measuring INR has drawbacks, the conventional INR remains a very viable means of expressing severity of liver disease and thus an integral part of the MELD score.

Keywords

Cirrhosis; liver transplantation; prognostic models; portal hypertension; survival

The Model for End-stage Liver Disease, created from a cohort of patients undergoing transjugular intrahepatic portosystemic shunts (1), has been demonstrated to be an excellent predictor of survival in patients with end-stage liver disease (2,3) The MELD score is derived from the International Normalized Ratio (INR) of prothrombin time, serum creatinine, and serum total bilirubin using the following formula:

$$\text{MELD} = 9.57 \times \ln(\text{cr}) + 3.78 \times \ln(\text{bili}) + 11.20 \times \ln(\text{INR}) + 6.43$$

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The major use of the MELD score in the United States, as also worldwide, is to prioritize allocation of organs for liver transplantation among patients with chronic liver disease. This is because of the proven ability of the MELD system to rank patients according to risk for 3 month mortality. Of the three variables in the MELD score, the INR carries the most weight. Therefore, it is important that the INR be measured reliably. An inappropriate determination of the INR would result in an incorrect MELD score, thereby putting some patients listed for liver transplantation at a disadvantage.

To understand the pitfalls in the determination of the INR it is necessary to know the basis on which the INR system was created. The INR is a way of mathematically transforming the prothrombin time in seconds to a ratio. It was hoped that this would eliminate the variation between laboratories in expressing the prothrombin time since patients on anticoagulation often obtained different readings from different laboratories.. The INR for prothrombin time is derived by dividing the patient's prothrombin time by a control mean normal prothrombin time (MNPT), and the product is raised to the international sensitivity index (ISI) for thromboplastin. The ISI is provided by the manufacturer and varies between 1 and 3 worldwide, with most thromboplastins currently available in the United States having an ISI closer to 1.

The INR system has been validated in patients on stable anticoagulation (6). The INR, however, has also been used in the place of the prothrombin time to determine severity of liver disease even though there is significant difference between the abnormalities in coagulation factors in patients with liver disease as compared to patients on Warfarin. In liver disease, there may be a deficiency in fibrinogen, prothrombin (Factor II), as well as Factors V, VII, IX and X and components of the anti-coagulant system such as protein C and protein S. On the other hand, patients on warfarin have a decrease only in the Vitamin K-derived factors, namely Factors II, VII, IX and X. Thus, patients with liver disease have a significantly more complex coagulopathy than patients on warfarin because they have, in addition, a defect in anti-coagulant factors, Factor V and possibly fibrinogen synthesis. The INR may vary in liver disease because of causes which are generic, and causes specific to liver disease (4,5).

Generic Causes of Variation in INR

Generic causes of variation in the INR are related to incorrect determination of the mean normal prothrombin time (MNPT), using an arithmetic mean rather than a geometric mean. There may also be differences in the sodium citrate concentration used to determine the ISI by the manufacturer as compared to the sodium citrate concentration used in the local laboratory. The ISI is typically calibrated for each reagent/instrument combination. Because different instruments use different endpoints (manual, photo-optical, or mechanical methods), an incorrect instrument /reagent combination will also give an erroneous ISI (7). There may also be an incorrect choice of the International Reference Preparation (IRP) for calibration of instruments, and this is demonstrated by laboratories noting an incorrect calibration of the commercial agent against the International Reference Preparation.

The International Sensitivity Index (ISI) is a major determinant of the INR. Each manufacturer determines the ISI of the thromboplastin in reference to a World Health Organization reference thromboplastin. There are over 25 different commercially available thromboplastins which need to be calibrated locally. If the INR results on certified plasmas produce an INR that is different from the certified plasma INR greater than 15%, the local system ISI should not be adopted. Moreover, the coefficient of variation between determinations should be 3% or less, and if this exceeds 3%, the locally calibrated ISI

cannot be considered valid. These important details are sometimes overlooked in laboratories which result in an incorrect INR determination.

Liver Specific Causes of Variation in INR

The liver specific causes of an incorrect INR are related to the fact that the ISI has been standardized for patients on warfarin therapy (see also the chapter by Tripodi in this volume). Since patients with liver disease have more complex coagulopathy, the ISI as calibrated for warfarin therapy may not be applicable to liver disease.

MELD as a Predictor of Survival

On the other hand, virtually every study that has looked at the MELD score as a predictor of survival has demonstrated that the MELD score using the INR with ISI calibrated for patients on warfarin has a 'c' statistic of approximately 0.8, indicating excellent discrimination. Although the current method of measuring INR has drawbacks, the INR is the only standardized method currently available within the United States for expressing the prothrombin time. Therefore, the INR, a reliable measure of prothrombin time in patients on anticoagulation, will also continue to be a means of expressing severity of liver disease.

As indicated earlier, the ISI is assigned to each batch of thromboplastin based on the prothrombin time in patients on warfarin anticoagulation. The ISI has not previously been calibrated based on prolongation of prothrombin time in patients with chronic liver disease. Two recent studies have demonstrated that if thromboplastins are calibrated using plasma from patients with cirrhosis (rather than plasma from patients on warfarin), the variability in measurement of the INR is largely eliminated (8,9). The MELD scores using the INR obtained with recalibrated ISI were more reproducible in the patients with cirrhosis who were studied.

A change to a laboratory system which uses an ISI calibrated to patients with liver disease is likely to eliminate to a great extent the variation from laboratory to laboratory currently noted in the INR. Therefore, significant changes need to be made in the laboratory community to have two different prothrombin times, one for patients on oral anticoagulation and the other for patients with liver disease (INR_{Vitamin K antagonists}, and INR_{liver}).

Summary

Currently, the ISI used in clinical laboratories to calculate the INR is not calibrated based on prolongation of prothrombin time in patients with chronic liver disease. As a result, variation in the conventionally measured INR (using warfarin-derived standards to determine the thromboplastin ISI) has been well-documented in liver disease patients. In spite of this limitation, virtually every study that has looked at the MELD score as a predictor of survival has demonstrated that the MELD score using the conventional INR possesses excellent survival discrimination. This fact, along with the wide availability of this relatively simple test, provides a strong argument for its continued use in survival estimations and thus organ allocation in advanced liver disease. Indeed, experts have recommended that the INR should not be removed from the MELD but rather it should be recalculated in patients with chronic liver disease. If the ISI is calculated from standards based on chronic liver disease to provide the INR_{liver}, it is likely to provide an even more accurate measurement. It is anticipated that in the future the variations in the prothrombin time and, therefore, the MELD score from laboratory to laboratory will be greatly reduced by incorporation of this technique. Meanwhile, the current MELD calculation using a conventionally determined INR remains a proven, valid and clinically useful tool in predicting survival in end stage liver disease.

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