Letter to the Editor

Response to *Comment on: Early recovery pathway for hepatectomy: data-driven liver resection care and recovery*

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Provenance: This is an invited Letter to the Editor commissioned by Editor-in-Chief Yilei Mao (Department of Liver Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China).

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We are grateful for the questions raised by Drs. Blasi and Beltran and appreciate the opportunity to respond (1). The comment on our article entitled *Early recovery pathway for hepatectomy*: *data-driven liver resection care and recovery* questions the recommendation that fresh frozen plasma (FFP) transfusion be used to correct coagulopathy based on international normalized ratio (INR) and clinical risk factors for coagulopathy in patients following liver resection (1,2). The following points are specifically raised:

(I) Prothrombin time (PT) expressed as INR helps assess liver function but not predict the risk of bleeding;
(II) Complete correction of PT by FFP transfusion is rarely achieved;
(III) Use of FFP is associated with a number of adverse effects;
(IV) Patients that undergo liver resection are at risk of venous thromboembolism (VTE);
(V) When PT indicates hypocoagulability, thromboelastometry reveals hypercoagulability.

Upon close review of the literature cited by Drs. Blasi and Beltran as well as additional studies, the authors would like to offer counterpoints and propose a compromise. The authors agree that there is insufficient evidence to conclude that abnormal coagulopathy studies involving PT and/or INR alone predict bleeding following liver resection (3). However, the relationship between thromboelastography (TEG) and VTE following liver resection or between TEG and post-operative hemorrhage for that matter has also yet to be established. While McCrath *et al.* have demonstrated that maximum amplitude (MA) of TEG predicts postoperative thrombotic complications including myocardial infarction in a heterogeneous surgical population with no clear standard use of post-operative VTE prophylaxis or risk stratification, there does not appear to be a prospective study of liver resection patients establishing such a predictive relationship (4). In one study that mentions correlation of TEG and deep vein thrombosis (DVT) in living donors undergoing right hepatectomies, only one patient was noted to have elevated TEG on post-op day 5 and developed a DVT on day 8 (5). However, in that protocol all patients received 2 units of FFP and 2 units of blood preoperatively (5). There is a published protocol for a pending well-designed meta-analysis of viscoelastic testing for hepatic surgery, however the analysis has yet to be published and the authors suspect that there will be insufficient studies to power such an analysis (6).

Regarding use of TEG techniques to measure coagulopathy, the authors agree that this is a more accurate means of assessing coagulopathy in many settings including the perioperative one. Nevertheless, one must be cautious when interpreting the available data. The respondents cite a number of studies detailing the virtues of rotational thromboelastometry (ROTEM) and TEG. Yet in the

supporting articles cited, the surgical procedures studied are widely varied with only one of the citations detailing strictly perioperative liver resection elastography measurement (7). Moreover, the currently available data contains many different methods and timings of lab draws for TEG. Even the term "ROTEM" in several citations used to support the argument of our respondents means some combination of extrinsically activated thromboelastometry (EXTEM), fibrinogen activity thromboelastometry (FIBTEM), maximum clot firmness (MCF) and intrinsically activated thromboelastometry (INTEM). This makes the results fairly difficult for clinicians inexperienced with viscoelastic testing to order and interpret absent accepted protocols.

While specialized intraoperative anesthesia understanding of TEG curves and physiology during major hepatectomy or liver transplants is extraordinarily useful in perioperative optimization, the values that would prompt action in the operating room may not mandate action in the post-operative setting. Stringent investigations are needed to establish solid parameters and protocols. Thus, while there is certainly no argument against use of TEG during liver transplantation and major liver resections to guide transfusion of blood products, there is far less of an understanding as to how or whether to employ TEG measurements in the post-operative setting. There does not appear to be concordance in the data regarding what to measure or when following liver resection. For instance, Gouvea *et al.* employed ROTEM techniques to measure living donors pre-operatively, at post-operative day one and at post-operative day three all via arterial line (7). Many patients undergoing liver resection no longer require arterial line at day three. Other protocols put forth in the trauma literature contain a mix of timings and use of rapid TEG at time of evaluation and 6 and 24 hours post-trauma (8,9). Moreover, these protocols defining use of TEG describe importance of interpretation of G value and MA values (8-10). The same level of standardization and understanding of nuance does not yet exist for post-hepatectomy patients.

Regarding over-administration of FFP, there is a paucity of large-scale evidence specific to the post-hepatectomy setting to unequivocally state that more liberal use of FFP causes overt harm. The group at Memorial Sloan Kettering attempted to address the question of FFP transfusion standards for patients undergoing liver resection for colorectal metastases in 2003 (11). They found that while there was an increase in complication rates on univariate analysis when FFP was used, when they factored in other complexities related to FFP transfusion, there was no significant difference on logistic regression, implying that the patients receiving FFP in the first place had a higher perioperative risk complex overall versus those who did not. More importantly, they identified only a 2% VTE rate and a 0.4% rate of return to operating room for hemorrhage (11). Even a study co-authored by Dr. Blasi demonstrated that elimination of routine FFP transfusion did not significantly change the overall Clavien-Dindo complication rate or the rates of re-intervention for bleeding, with DVT rate not reported in the manuscript (12). The authors are willing to evolve, but with evidence that addresses the question at hand. Drs. Blasi and Beltran seem to imply that over-use of FFP in an INR-implied hypocoagulable state that is instead a TEG- or ROTEM-implied hypercoagulable state might increase the rate of thromboembolic events following hepatectomy. The authors are unaware of data to support such an assumption. While there are data to suggest that increased transfusion of blood products including FFP can result in harm in heterogeneous critically ill and trauma patient populations, the authors are not aware of conclusive data to that effect in the post-hepatectomy population.

It should be noted that the authors agree with the points made by the respondents regarding use of chemical VTE prophylaxis. There is sufficient data to suggest reduction of VTE without increase in takebacks for bleeding, and it is our standard practice to employ post-operative VTE prophylaxis without reservation (13). That said, we do not agree that the same level of evidence supports elimination of FFP use altogether. Takeback for liver hemorrhage can have catastrophic consequences and is regarded as a "never event" by many surgeons. We acknowledge that in our quest to avoid such a complication, it is easy to have liberal transfusion thresholds. This emphasizes the importance of evidence-based guidelines. The authors wonder what Drs. Blasi and Beltran would advocate for a patient with marked thrombocytopenia following many rounds of chemotherapy, who has 30% functional liver remnant and a rising INR on post-operative day one? While the authors understand that in the future, we may be able to use TEG-derivatives to know exactly what product(s) to give a patient like this, that technology is not currently widely available or easy to interpret. We concede that our transfusion thresholds may change dramatically in the coming years as data regarding use of ROTEM and TEG interpretations after liver resection becomes more powerful. While we agree that judicious use of FFP is warranted and that decreased use can reduce costs without negatively altering outcomes, we also find the current evidence inadequate to support

creation of guidelines for use of ROTEM or TEG to guide post-hepatectomy transfusion (or anticoagulation). The authors invite Drs. Blasi and Beltran to propose a protocol for perioperative monitoring employing thromboelastometry, including timing and technique of lab draw and interpretation, as well as transfusion and anticoagulation triggers. Such a protocol could then be externally validated and adopted worldwide. The authors would be happy to offer their center as a testing site and help to coordinate a multi-institutional trial to validate such a protocol in a randomized setting. The authors thank Drs. Blasi and Beltran for initiation of this timely discussion.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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