the significant impact of perioperative AKI on post-LT outcomes [2], every attempt to prevent and reverse it in a timely manner should be made.

Leithhead and Ferguson also suggest to cautiously interpret our finding concerning the lack of increase in post-LT CKD in the MELD era, which is discordant with other studies of the national database [3]. While registry databases provide a large sample size, they are limited by available data (e.g., measured GFR), lack of standardization (e.g., assay for serum creatinine), and completeness (e.g., loss to follow-up). As a single centre study, we can only report what we observed in our patients – post-transplant CKD is clearly an important comorbidity; whether our practice of vigilant monitoring and early intervention was responsible for the lack of the trend observed in other studies, remains uncertain.

It may be worth noting that the organ allocation system should not affect the biological incidence of renal morbidity in transplant candidates. The primary reason that more patients are transplanted with reduced renal function is the worsening organ shortage, which results in more patients developing complications of advanced cirrhosis, such as hepatorenal syndrome and AKI. The MELD score identifies these patients as their renal function deteriorates and facilitates access to LT. Should renal function not be a part of the allocation scheme, further progression of renal dysfunction would result in increased requirements for simultaneous kidney transplantation or higher rates of withdrawal from the waiting list. The net effect of the MELD-based allocation may be a reduction in these poor waitlist outcomes at the expense of an increase in incidence of end-stage renal disease (ESRD), although our data did not show this trend.

Lastly, we agree that directly measured GFR is not a convenient way to monitor our patients long-term. However, we do believe that clinicians tend to underutilize other measures of GFR, such as creatinine clearance or serum cystatin-C. Likewise, an important message in this paper is that serum creatinine or estimated GFR (often automatically reported by the laboratory) should not be interpreted in isolation. Changes over time in creatinine or eGFR may help the astute clinician to identify or at least suspect CKD. Unfortunately, the current CKD classification [4] does not encompass changes in serum creatinine and the diagnosis of CKD may be missed, due to absent vigilance of the transplant physician.

### Conflict of interest

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### References


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**To the Editor:**

We read with great interest the randomized controlled trial (RCT) by Perarnau et al. that was published in the *Journal of Hepatology* [1]. The first RCT on transjugular intrahepatic portosystemic shunt (TIPS), comparing PTFE-covered stents (CS) with bare stents (BS) on shunt patency and clinical outcomes, was published in 2004 [2]. Ten years later, Perarnau et al. concluded that CS provided a significant reduction in shunt dysfunction compared to BS. No doubt, this paper has provided additional evidence to confirm the advantages of CS. However, we still believe that certain issues merit further discussion.

To begin with, the shunt dysfunction rates in this paper (31.5% and 44.0% in the CS group vs. 53.8% and 63.6% in the BS group after 1 and 2 years) were higher than those in the first RCT (12.8% and 34% in the CS group vs. 43.9% and 74% in the BS group after 1 and 2 years) [1,2]. The authors attribute the outcome variance to differences in patient selection and shunt diameter [1]. However, this explanation may be incomplete. For example, the...
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position of the stent may also influence the outcome of TIPS. A frequency of approximately 20% proximal or distal displacement was given in the previous American Association for the Study of Liver Disease (AASLD) guidelines [3]. We also found that stent displacement may lead to a higher risk of shunt dysfunction in patients with variceal bleeding [4]. To illustrate the impact of stent position, we present the following case: A 62-year-old woman with a history of decompensated hepatitis B-related cirrhosis was admitted in our department to undergo TIPS insertion for the treatment of variceal bleeding. The portosystemic gradient decreased from 26 mmHg to 10 mmHg after the implantation of a 8/80 mm Fluency covered stent (Bard, Peripheral Vascular, Tempe, AZ, USA) (Fig. 1A) on April 17th, 2013. However, the patient developed variceal bleeding again on April 19th, 2013. Haemoglobin dropped from 99 g/L to 90 g/L, gastroesophageal varices and red-signs were seen during upper endoscopy. Direct portography confirmed that the top of the stent stood out against the upper wall of the right hepatic vein (Fig. 1B), raising the portosystemic gradient to 16 mmHg as a result. A new stent was inserted to extend the shunt to the junction of the hepatic vein and inferior vena cava (Fig. 1C). After TIPS revision, the portosystemic pressure gradient decreased to 10 mmHg, and the symptoms disappeared. The patient was free of variceal re-bleeding after one year of follow-up. Thus, the results could be cofounded by several factors if shunt dysfunction is used as the primary end point.

Secondly, dysfunction was defined by the authors as an increase in the portosystemic pressure gradient (PPG) to ≥12 mmHg and/or a reduction in the calibre of the stent by ≥50% at portography [1]. However, the definition of shunt dysfunction may differ depending on the underlying liver disease (i.e. ascites, haemorrhage), which may result in different risks of shunt dysfunction [5]. We reviewed previous RCTs in TIPS, and found that RCTs about haemorrhage defined shunt dysfunction in one or several of the following criteria: (1) Doppler sonography: a 20–50% decrease in the stent flow, a portal blood-flow velocity lower than 10–60 cm/s or over 120 cm/s, or a change in the direction of the flow in the infrahepatic portal branches; (2) Angiography: a reduction in the calibre of the stent by ≥50% or an occlusion of the shunt; (3) PPG: over 12–15 mmHg. Meanwhile RCTs on ascites identified shunt dysfunction through angiographic findings and a PPG over 12 mmHg except Doppler sonography. Thus, no consistent agreement has been reached among researchers as to the exact judgment criteria of shunt dysfunction. Notably, most physicians rely on Doppler sonography to monitor shunt dysfunction in practice, but the best indicator of shunt dysfunction is symptom recurrence according to the AASLD guidelines [6]. Furthermore, if shunt dysfunction occurs, what actions should be taken? Treatments, such as balloon angioplasty or new stent insertion were provided if shunt dysfunction was confirmed by the author [1], even though such interventions may not conform to the clinical reality. In practice, TIPS revision is only performed when symptoms occur [7]. Hence, the definition and management of shunt dysfunction still needs further exploration, and symptom recurrence may be more relevant to both clinical practice and scientific studies than shunt dysfunction.

Therefore, shunt dysfunction may not be the suitable primary end point of TIPS trials. From our perspective, the best primary end point should be the problem for which the management was conducted. The recurrence of symptoms, such as variceal bleeding and hepatic ascites, may be considered the optimal primary end point. Thus, we use symptom recurrence to define shunt dysfunction in our study [8]. We look forward to further discussions regarding the optimal primary end point of TIPS research.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Reply to: “Shunt dysfunction: Is it suitable as the primary end point in transjugular intrahepatic portosystemic shunt trials?”

To the Editor:
We are very honoured by the interest of Han and colleagues for our study [1]. In their letter two topics were discussed. The first topic was the type of dysfunction in which they underlined and illustrated the risk of initial stent malposition. The second topic was in relation with the primary end point of our study. Here, they suggested the use of clinical recurrence rather than haemodynamics, to qualify shunt dysfunction.

Concerning the first point, we noticed that stenoses were mainly located at the upper end of the TIPS and at the hepatic vein, with cumulative rates of 63.7% with covered stents and 70.5% with bare stents. A great majority of new stent insertion and redilation procedures were performed at the first six-month scheduled control. This can effectively address an initial stent malposition, as described in this interesting case by our Chinese colleagues. This case report illustrates well how difficult it is, during the initial procedure, to adjust the upper side of the TIPS to the vena cava. It is also difficult to avoid the straightening of the stent against the hepatic vein wall when withdrawing the inside catheter. There is no reason why this problem would occur with a certain type of stent and influence the results of our comparative trial. Furthermore, as our study was multi-centred, this minimized the influence of operator dependent bias.

The second point is more disputable. In our study, the primary end point was to compare short and long term patency of bare and covered stents independently of their efficiency on symptoms. As the recurrence of symptoms, which was our secondary end point, seldom occurred (twelve in all), it was not used as a discriminator. Variable delay between haemodynamic dysfunction and clinical recurrence, severity of underlying cirrhosis, or potential reversibility of some liver diseases explain that shunt dysfunction and bleeding recurrence are not identical. Thus, symptom recurrence may not occur despite the presence of shunt dysfunction when the porto-caval gradient can be reduced after alcohol withdrawal or virus clearance. Furthermore, we would like to point out three arguments in favour of haemodynamic criteria.

First, ascites recurrence does not expose patients to a death risk, unlike variceal rebleeding. Rebleeding is observed in 20% of cases with bare stents [2], and in 10% with covered stents. These events have a proper mortality rate as described by other teams [3–5], which can be estimated at 6% [6]. Waiting for a symptom to occur is harmful in term of mortality. We have made the choice to continue to detect shunt dysfunction as early as possible especially for bleeding indications.

Second, the delay between shunt dysfunction and symptom recurrence depends on so many parameters that it seems impossible to anticipate. A TIPS which has been completely thrombosed for a long time, can be technically difficult to recanalize. Sometimes it is impossible and we need to perform a new TIPS besides the old one. This is why then we prefer to detect and correct dysfunction early before complete occlusion. The problem lies in the early detection of shunt dysfunction and we agree with Cai et al. that Doppler is not a confident method for screening. In an ancillary study of STIC-TIPS (submitted paper) we compared different Doppler parameters without finding a good sensitive and specific marker of dysfunction. Perhaps, as suggested by Rössle, a parameter combining endoscopy and Doppler could provide this faithful alarm we need to detect TIPS dysfunction [7].

Third, we are not convinced that clinical criteria should replace haemodynamic criteria in studies dedicated to TIPS in general. To our knowledge, sensitivity and specificity of symptom recurrence to diagnose impaired TIPS patency has not been studied previously and many confounding variables can interfere with the diagnosis i.e.: ascites recurrence may be due to either salt or water restriction modification, diuretic variation, cardiac or renal failure. For multicentre studies non-questionable criteria are essential and haemodynamic parameters validate this condition in our opinion. Hepatic venous pressure gradient (HVPG) is considered as the gold standard for portal hypertension measurement. When Cai et al. checked the patency of their TIPS, they observed a raise of the portosystemic pressure gradient to 16 mmHg.

Of course, studies exploring the efficacy of TIPS upon different complications of portal hypertension should have as end point the clinical recurrence of the indication for TIPS. But we had a different goal, which was to compare the patency of bare and covered stents used to perform TIPS.

Finally, it may be important to discuss the need of a systematic angiographic TIPS control after 6 months (or earlier) to correct malposition of the TIPS. Randomized studies about TIPS treatment or conventional treatment of variceal bleeding or ascites should always have recurrence of indication as a clinical end point. Randomized controlled trials about methods to treat portal...