Aspirin improves transplant-free survival after TIPS implantation in patients with refractory ascites: a retrospective multicentre cohort study

Leon Louis Seifert1 · Philipp Schindler2 · Lukas Sturm3 · Wenyi Gu4 · Quentin Edward Seifert5 · Jan Frederic Weller6 · Christian Jansen7 · Michael Praktikno7 · Carsten Meyer8 · Martin Schoster1 · Christian Wilms1 · Miriam Maschmeier1 · Hartmut H. Schmidt1 · Max Masthoff2 · Michael Köhler2 · Michael Schultheiss3 · Jan Patrick Huber3 · Dominik Bettinger3 · Jonel Trebicka4 · Moritz Wildgruber2,9 · Hauke Heinzow1,10

Received: 19 November 2021 / Accepted: 14 March 2022 / Published online: 5 April 2022 © The Author(s) 2022

Abstract
Background and aims Transjugular intrahepatic portosystemic shunt (TIPS) implantation is an established procedure to treat portal hypertension. Impact of administration of aspirin on transplant-free survival after TIPS remains unknown.

Methods A multicenter retrospective analysis including patients with TIPS implantation between 2011 and 2018 at three tertiary German Liver Centers was performed. N=583 patients were included. Survival analysis was performed in a matched cohort after propensity score matching. Patients were grouped according to whether aspirin was (PSM-aspirin-cohort) or was not (PSM-no-aspirin-cohort) administered after TIPS. Primary endpoint of the study was transplant-free survival at 12 months after TIPS.

Results Aspirin improved transplant-free survival 12 months after TIPS with 90.7% transplant-free survival compared to 80.0% (p = 0.001) after PSM. Separated by TIPS indication, aspirin did improve transplant-free survival in patients with refractory ascites significantly (89.6% vs. 70.6% transplant-free survival, p < 0.001), while no significant effect was observed in patients with refractory variceal bleeding (91.1% vs. 92.2% transplant-free survival, p = 0.797).

Conclusion This retrospective multicenter study provides first data indicating a beneficial effect of aspirin on transplant-free survival after TIPS implantation in patients with refractory ascites.

Keywords Transjugular intrahepatic portosystemic shunt · Decompensated liver cirrhosis · Complications of liver cirrhosis · Portal hypertension · Ascites · Variceal bleeding · Liver transplantation · Hepatic decompensation · Thrombocyte aggregation inhibition · Aspirin · Propensity score matching

Abbreviations β Regression coefficient
FIPS Freiburg-index of post-TIPS survival

HCC Hepatocellular carcinoma
HE Hepatic encephalopathy
HR Hazard ratio

Leon Louis Seifert leonlouis.seifert@ukmuenster.de
1 Medical Clinic B, Department of Gastroenterology, Hepatology, Endocrinology, Infectiology, University Hospital Muenster, 48149 Muenster, Germany
2 Clinic for Radiology, University Hospital Muenster, 48149 Muenster, Germany
3 Department of Medicine II, Medical Center University of Freiburg, University of Freiburg, 79106 Freiburg, Germany
4 Department of Internal Medicine I, University Hospital Frankfurt, 60596 Frankfurt, Germany
5 Georg-August University of Goettingen, 37073 Goettingen, Germany
6 Department of Hematology, University Hospital Tuebingen, 72076 Tuebingen, Germany
7 Department of Internal Medicine I, University Hospital Bonn, 53127 Bonn, Germany
8 Department of Radiology, University Hospital Bonn, 53127 Bonn, Germany
9 Department of Radiology, University Hospital LMU Munich, 81377 Munich, Germany
10 Department of Internal Medicine I, Krankenhaus der Barmherzigen Brüder, 54292 Trier, Germany

Springer
INR  International normalized ratio  
LTX  Liver transplantation  
MELD  Model for end-stage liver disease  
m  Matched  
NAFLD  Non-alcoholic fatty liver disease  
NASH  Non-alcoholic steatohepatitis  
PSG  Portosystemic pressure gradient  
PSM  Propensity score matching  
PTFE  Polytetrafluoroethylene  
SD  Standard deviation  
SE  Standard error  
TFS  Transplant-free survival  
TIPS  Transjugular intrahepatic portosystemic shunt  
95% CI  95% Confidence interval

**Introduction**

Transjugular intrahepatic portosystemic shunt (TIPS) is performed to reduce portal hypertension and associated complications in patients with decompensated liver cirrhosis [1–3]. The procedure is safe with low rates of complication as a result of major progress in experience and technical ameliorations throughout the last decades [4]. In patients with refractory ascites, TIPS implantation improves transplant-free survival (TFS) and shows superior results of repetitive large volume paracentesis [5–7]. Concerning variceal bleeding, preemptive TIPS implantation should be considered in case of recurrent variceal bleeding as well as acute variceal bleeding [3, 8–10]. Both the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Disease (AASLD) recommend TIPS implantation when complications of portal hypertension are present in selected patients [11, 12]. Polytetrafluoroethylene-(PTFE-)covered stents have improved patency and overall survival compared to the use of bare-metal-stents (BMS) [13]. However, maintaining long-term patency of TIPS remains challenging. Approximately, one-third of patients require invasive TIPS revision to maintain or restore PTFE-shunt-patency within 2 years after placement [13–15]. Shunt stenosis or occlusion mostly occur due to a combination of parenchymal compression, thrombosis formation (acute and chronic) and neointimal hyperplasia [16, 17]. Common guidelines to maintain shunt patency via platelet inhibition or anticoagulative medication are lacking except for patients with portal vein thrombosis or Budd–Chiari syndrome as indication for TIPS [18]. Published experiences and studies are restricted to the era of non-covered stents [19, 20]. Potential beneficial effects of platelet inhibition after in TIPS placement are not sufficiently investigated. With acetalsalicylate acid (aspirin) being established in multiple indications after stent-implantation in the arterial system, little is known about the effect of platelet inhibition in the portal venous system. Administration of aspirin has been shown to be safe in cirrhotic patients [21]. The standardized use of aspirin following TIPS implantation implies potential to reduce TIPS dysfunction and improve post-TIPS survival. Currently, aspirin and other platelet inhibitors are routinely used after TIPS implantation while scientific evidence is lacking [18]. We, therefore, aimed to investigate the effect of aspirin on transplant-free survival (TFS) in patients with TIPS placement in a large retrospective patient cohort.

**Methods**

**Study design**

Primary endpoint of this retrospective multicenter study was the impact of aspirin on transplant-free survival at 12 months after TIPS implantation.

**Data collection**

Patient data from three tertiary care medical centers (University Clinic of Muenster, University Clinic of Bonn, University Medical center of Freiburg, to be called center A, B and C by random assignment) were included. Data were collected retrospectively from all patients in whom TIPS implantation was performed in the institutions between 2011 and 2018. Patient data were collected via electronic record review. Data of a total of 814 patients were available. Laboratory and clinical data before TIPS implantation were assessed within 3 days before TIPS. Follow-up data were collected until death, liver transplantation or end of follow-up.

For further analysis, inclusion and exclusion criteria were applied (see Fig. 1). All patients receiving TIPS insertion for refractory ascites (defined as ascites refractory to escalated therapy with diuretics and large volume paracentesis) and/or recurrent or refractory esophageal variceal bleeding were included. Patients with other indication for TIPS insertion were excluded. All patients with vascular etiology of liver disease were excluded as well as all patients with full anticoagulation therapy or a history of liver transplantation. Only adult patients (age ≥ 18) in whom PTFE-covered stents (Viatorr. W.L. Gore USA or BeGraft peripheral, Bentley, Hechingen, Germany) were used were included. Transplant-free survival was defined as survival free of death of any cause of liver transplantation. Only adult patients (age ≥ 18) in whom PTFE-covered stents (Viatorr. W.L. Gore USA or BeGraft peripheral, Bentley, Hechingen, Germany) were used were included. Transplant-free survival was defined as survival free of death of any cause of liver transplantation. Baseline patient characteristics are presented in Table 1. Administration of aspirin was only performed at institutions A and C as routine care after TIPS implantation if platelet count was > 50 000/μl. Institution B did not administer aspirin following TIPS. Aspirin dosage was 100 mg orally once per day in all patients. Treatment...
was initiated within 72 h after TIPS implantation irrespective of TIPS indication.

**TIPS procedure**

TIPS placement was performed by experienced interventional radiologists and/or gastroenterologists in accordance with standard operating procedures at the respective study center. Sonographic guidance was used during the TIPS procedure to control the intrahepatic needle position while gaining access to the portal vein. Portosystemic pressure gradient measurements were done in course of the intervention before and after TIPS implantation to confirm successful reduction of the pressure gradient after TIPS placement. Technical procedures and success rates did not differ between the institutions.

**Statistical analysis**

Statistical analyses were performed using SPSS version 26.0 (SPSS Inc., Chicago, Illinois, USA) as well as R version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria). All data are presented as the mean (SD), median (range), absolute or percentage, depending on nature of variables and distribution. Chi-square test was used for contingency tables. Paired student t-test was used for quantitative and Mann–Whitney U test was used for qualitative data with non-normal distribution. Two-sided p-values < 0.05 were defined as statistically significant.

For analysis of transplant-free survival after 12 months logistic regression models were created. Variables were consecutively included in a multivariable Cox regression analysis if they were significantly associated with 12-month transplant-free survival in univariate regression model (see Table 2). Multivariable Cox-regression analysis was performed using forward variable selection. For further analysis, we performed propensity score matching (PSM). PSM was performed after logistic regression analysis to create a propensity score for each patient. Age, bilirubin, creatinine, INR and MELD score were identified as suitable variables for PSM (p < 0.001). Sex was included to adjust for gender differences. Finally, PSM was performed entering the following variables: age, sex, MELD-score and platelet count. Age, sex and MELD score were included as matching parameters as they included all independent predictors of transplant-free survival identified via logistic and multivariate regression analysis. No significant differences were found if using bilirubin, creatinine and INR or MELD score as matching parameters combined with age and sex. Platelet count was included in further optimization of the matching. Subsequently, a case–control match between patients who received aspirin and patient who did not was obtained by use of nearest-neighborhood-matching using a caliper width of 0.2 without replacement as described elsewhere [22, 23]. A matching ratio of 1:1 was used. Baseline characteristics after PSM are presented in Table 3. Kaplan–Meier curves and the log-rank test were used to analyze the impact on transplant-free survival in the matched cohort.
| Parameter                          | All patients | Aspirin | No-aspirin | p-Value |
|-----------------------------------|--------------|---------|------------|---------|
|                                   | % (% total number) | % (% total number) | % (% total number) |         |
|                                   | median/mean (SD) | median/mean (SD) | median/mean (SD) |         |
| n° of patients                    |               |         |            |         |
| Center                            |               |         |            | <0.001  |
| A                                 | 26.4% (153)   | 34.2% (55) | 23.2% (98)  |         |
| B                                 | 27.2% (159)   |         | 37.7% (159) |         |
| C                                 | 46.4% (271)   | 65.8% (106) | 39.1% (165) |         |
| Sex                               |               |         |            | 0.712   |
| Male                              | 62.8% (366)   | 64.0% (103) | 62.3% (263) |         |
| Female                            | 37.2% (217)   | 36.0% (58)  | 37.7% (159) |         |
| Age (median, range, in years)     | 59 (18–84)    | 59 (21–81)  | 59 (18–84)  | 0.081   |
| PTFE-covered stent                | 100% (583)    | 100% (161)  | 100% (422)  |         |
| Etiology of liver disease         |               |         |            | 0.292   |
| Alcoholic                         | 58.0% (339)   | 58.4% (94)  | 58.1% (245) |         |
| Viral                             | 11.1% (65)    | 7.5% (12)   | 12.6% (53)  |         |
| NAFLD                             | 8.9% (52)     | 10.6% (17)  | 8.3% (35)   |         |
| Other                             | 21.9% (127)   | 23.6% (38)  | 21.1% (89)  |         |
| Child–Pugh grade                  |               |         |            | 0.028   |
| A                                 | 21.7% (127)   | 23.1% (37)  | 21.1% (90)  |         |
| B                                 | 59.4% (345)   | 65.0% (104) | 57.2% (241) |         |
| C                                 | 18.9% (110)   | 11.9% (19)  | 21.6% (91)  |         |
| Indication for TIPS               |               |         |            | 0.121   |
| Ascites                           | 62.3% (364)   | 65.8% (106) | 61.1% (258) |         |
| Variceal bleeding                 | 29.6% (172)   | 29.8% (48)  | 29.4% (124) |         |
| Both                              | 8.0% (47)     | 4.3% (7)    | 9.5% (40)   |         |
| LTX prior TIPS                    |               |         |            |         |
| Yes                               |               |         |            | 0.226   |
| No                                | 100% (583)    | 100% (161)  | 100% (422)  |         |
| HE prior TIPS                     |               |         |            |         |
| Yes                               | 17.5% (102)   | 14.3% (23)  | 18.6% (81)  |         |
| No                                | 82.5% (481)   | 85.7% (138) | 81.4% (341) |         |
| Diabetes                          |               |         |            | 0.018   |
| Yes                               | 32.6% (190)   | 26.0% (58)  | 31.5% (133) |         |
| No                                | 67.4% (393)   | 64.0% (103) | 68.5% (289) |         |
| Aspirin                           |               |         |            | <0.001  |
| Yes                               | 27.6% (161)   | 100% (161) | –           |         |
| No                                | 72.4% (422)   | 100% (422) | –           |         |
| Anticoagulative regimens          |               |         |            |         |
| Yes                               |               |         |            |         |
| No                                | 100% (538)    | 100% (161)  | 100% (422)  |         |
| MELD-score                        | 12.3 (4.9)    | 11.9 (3.8)  | 12.6 (5.3)  | 0.001   |
| MELD-sodium-score                 | 14.0 (5.9)    | 14.0 (4.9)  | 14.0 (6.3)  | 0.119   |
| FIPS                              | 0.08 (1.44)   | 0.03 (1.62) | 0.10 (1.31) | 0.001   |
| Bilirubin (mg/dl)                 | 1.40 (1.59)   | 1.39 (0.96) | 1.42 (1.75) | <0.001  |
| Albumin (g/dl)                    | 3.50 (3.9)    | 3.7 (3.2)   | 3.6 (4.2)   | <0.001  |
| Creatinine (mg/dl)                | 1.06 (0.87)   | 1.05 (0.63) | 1.07 (0.95) | 0.182   |
| INR                               | 1.22 (0.23)   | 1.21 (0.24) | 1.24 (0.18) | <0.001  |
| Platelets (cells/µl)              | 135 000 (82)  | 145 000 (90) | 133 (75)   | <0.001  |
| Hemoglobin (mg/dl)                | 10.2 (2.2)    | 10.4 (2.3)  | 10.1 (2.2)  | 0.028   |
| PSG (mmHg)                        | 19.0 (6.0)    | 19.1 (5.1)  | 19.0 (6.3)  | 0.086   |
Results

All available patient data from patients receiving TIPS implantation from the three participating institutions were collected (n = 814 patients). After application of exclusion and inclusion criteria, data of a total of 583 patients were included in the final analysis as presented in Fig. 1. Baseline characteristics of the entire patient cohort are presented in Table 1 and separated by institution in supplementary Table 1.

To identify independent risk factors associated with impaired transplant-free survival after TIPS implantation, we performed multivariate Cox regression analysis using forward variable selection with all variables that were significantly associated with 12-month transplant-free survival in univariable regression analysis. Concerning laboratory parameters before TIPS placement, we identified increased levels of bilirubin (p < 0.001), creatinine (p < 0.001) and higher age (p < 0.001) as risk factors for death or liver transplantation after TIPS, whereas administration of aspirin (p < 0.001) is an independent predictor of transplant-free survival at 12 months (see Table 2).

Due to significant differences between patients who received aspirin and did not (see Table 1), comparison of transplant-free survival in a matched patient-cohort was necessary to investigate the beneficial effect of aspirin on transplant-free survival. We performed propensity score matching analysis using age, sex, MELD-score and platelet count as matching parameters. The baseline characteristics of the matched patient cohort are presented in Table 3. Patients were grouped based on aspirin administration (PSM-aspirin-cohort, PSM-no-aspirin-cohort). There were no significant differences concerning etiology or severity of liver disease in the matched patient cohort. Satisfactory balance of respective variables is indicated by Cohen’s d.

Kaplan–Meier analysis shows superior transplant-free survival in patients who received aspirin after TIPS implantation (p = 0.001, log-rank test; see Fig. 2). In the PSM-aspirin-cohort, 97.6%, 95.8% and 90.7% patients achieved transplant-free survival at 3, 6 and 12 months after TIPS implantation, respectively, compared to 90.2%, 87.6% and 80.0% in the PSM-no-aspirin-cohort. Transplant-free survival did not differ significantly between the different centers included irrespective of aspirin administration (p = 0.424 and p = 0.272 respectively, log-rank test). Improvement of transplant-free survival by aspirin was pronounced in more severe cirrhosis (Child B and C cirrhosis, p = 0.007, log-rank test; see supplementary Fig. 1B) compared to patients with Child A cirrhosis (p = 0.064, log-rank test; see supplementary Fig. 1A).

Survival rates are distinct by TIPS indication. Baseline characteristics according to TIPS indication in the matched cohort are presented in supplementary tables 2 and 3. In patients with refractory ascites as indication for TIPS implantation (total n = 191 patients; 98 PSM-aspirin-cohort, 93 PSM-no-aspirin cohort), administration of aspirin shows significant improvement of transplant-free survival after 12 months (89.6% in the PSM-aspirin-cohort, 70.6% in the PSM-no-aspirin-cohort, p < 0.001, log-rank test; see Fig. 3a). On the other hand, transplant-free survival was
Table 3  Baseline characteristics grouped by aspirin administration after PSM

| Parameter                          | Aspirin-group % (total number) or median/mean (SD) | No-aspirin-group % (total number) or median/mean (SD) | Cohen’s $d$ | $p$-value |
|-----------------------------------|--------------------------------------------------|------------------------------------------------------|------------|-----------|
| n° of patients                    | 50% (150)                                        | 50% (150)                                            | –          | < 0.001   |
| Center                            |                                                  |                                                     |            |           |
| A                                 | 34.0% (51)                                       | 21.3% (32)                                           | –          |           |
| B                                 | –                                                | 39.3% (59)                                           | –          |           |
| C                                 | 66.0% (99)                                       | 39.3% (59)                                           | –          |           |
| Sex                               |                                                  |                                                     | 0.073      | 0.633     |
| Male                              | 64.0% (96)                                       | 61.3% (92)                                           |            |           |
| Female                            | 34.0% (54)                                       | 38.7% (58)                                           |            |           |
| Age (median, range, in years)     | 60 (21–81)                                       | 60 (26–82)                                           | − 0.021    | 0.811     |
| PTFE-covered stent                | 100% (150)                                       | 100% (150)                                           | –          | –         |
| Etiology of liver disease         |                                                  |                                                     | 0.109      | 0.941     |
| Alcoholic                         | 58.0% (87)                                       | 57.3% (86)                                           |            |           |
| Viral                             | 8.0% (12)                                        | 10.0% (15)                                           |            |           |
| NAFLD                             | 10.9% (15)                                       | 10.0% (15)                                           |            |           |
| Other                             | 24.0% (36)                                       | 22.7% (34)                                           |            |           |
| Child–Pugh grade                  |                                                  |                                                     | 0.029      | 0.246     |
| A                                 | 24.0% (36)                                       | 28.2% (42)                                           |            |           |
| B                                 | 64.0% (96)                                       | 61.7% (92)                                           |            |           |
| C                                 | 12.0% (18)                                       | 10.1% (18)                                           |            |           |
| Indication for TIPS               |                                                  |                                                     | 0.043      | 0.371     |
| Ascites                           | 65.3% (98)                                       | 62.0% (93)                                           |            |           |
| Variceal bleeding                 | 30.7% (46)                                       | 29.3% (44)                                           |            |           |
| Both                              | 4.0% (6)                                         | 8.7% (13)                                            |            |           |
| LTX prior TIPS                    |                                                  |                                                     | 0.077      | 0.665     |
| Yes                               | –                                                | –                                                    |            |           |
| No                                | 100% (150)                                       | 100% (150)                                           |            |           |
| HE prior TIPS                     |                                                  |                                                     | 0.080      | 0.690     |
| Yes                               | 13.3% (20)                                       | 14.0% (21)                                           |            |           |
| No                                | 86.7% (130)                                      | 86.0% (129)                                          |            |           |
| Diabetes                          |                                                  |                                                     | 0.031      | 0.267     |
| Yes                               | 36.7% (55)                                       | 34.0% (54)                                           |            |           |
| No                                | 63.3% (95)                                       | 64.0% (96)                                           |            |           |
| Platelet inhibitors               |                                                  |                                                     | –          | < 0.001   |
| Yes                               | 100% (150)                                       | –                                                    |            |           |
| No                                | –                                                | 100% (150)                                           |            |           |
| Anticoagulative regimens          |                                                  |                                                     | –          | –         |
| Yes                               | –                                                | –                                                    |            |           |
| No                                | 100% (150)                                       | 100% (150)                                           |            |           |
| MELD-score                        | 11.7 (3.5)                                       | 11.7 (3.6)                                           | < 0.001    | 0.819     |
| MELD-sodium-score                 | 14.1 (4.7)                                       | 13.4 (5.4)                                           | 0.138      | 0.244     |
| FIPS                              | − 0.22 (0.86)                                    | − 0.23 (0.96)                                        | − 0.011    | 0.883     |
| Bilirubin (mg/dl)                 | 1.36 (0.96)                                      | 1.42 (0.86)                                          | − 0.066    | 0.418     |
| Albumin (g/dl)                    | 3.6 (3.2)                                        | 3.7 (3.3)                                            | − 0.031    | 0.670     |
| Creatinine (mg/dl)                | 1.04 (0.58)                                      | 1.02 (0.61)                                          | 0.034      | 0.734     |
| INR                               | 1.21 (0.18)                                      | 1.21 (0.17)                                          | < 0.001    | 0.695     |
| Platelets (cells/µl)              | 159 000 (82)                                     | 159 000 (67)                                         | < 0.001    | 0.756     |
| Hemoglobin (mg/dl)                | 11.2 (3.6)                                       | 10.8 (2.3)                                           | 0.13       | 0.336     |
| PSG (mmHg)                        | 19.2 (5.1)                                       | 20.0 (5.9)                                           | − 0.14     | 0.130     |
not significantly affected in patients with variceal bleeding as TIPS indication (total n = 90 patients; 46 PSM-aspirin-cohort, 44 PSM-no-aspirin cohort) with a survival rate of 91.1% in the PSM-aspirin-cohort compared to 92.2% in the PSM-no-aspirin-cohort (p = 0.797, log-rank test; see Fig. 3b). No significant effect of aspirin was observed in patients in whom TIPS indication was not clearly distinguishable between refractory ascites and refractory variceal bleeding (total n = 19 patients; 6 PSM-aspirin-cohort, 13 PSM-no-aspirin cohort) (p = 0.297, log-rank test, data not visualized).

Discussion

This multicenter retrospective study found a beneficial effect of aspirin on transplant-free survival in patients who received TIPS implantation in a real-life cohort including 583 patients from three major German tertiary care liver centers. Aspirin was associated with a significant superior transplant-free survival within the first 12 months after TIPS implantation. We confirmed these findings through a robust matching using propensity score matching method. No significant differences concerning established parameters of liver function (Child–Pugh score, MELD-score) or recently introduced parameters of survival after TIPS implantation (FIPS-score) was found between the created cohorts [24]. The beneficial effect of aspirin is dependent from the underlying TIPS indication since transplant-free survival was improved in patients with refractory ascites but not in patients with variceal bleeding.

To the best of our knowledge, there are no published studies that investigate the effect of aspirin on transplant-free survival in the era of PTFE-covered stents. The question of whether to administer anticoagulation medication or platelet inhibitors to prevent TIPS associated complications remains unanswered and respective strategies differ immensely [18]. The effects of prophylactic anticoagulation by administration of low molecular weight heparin (enoxaparin or nadroparin) after TIPS-implantation are currently under investigation in a prospective study [25]. Current published evidence in this field is sparse and not sufficient to develop reliable recommendations.

In stent placement in arterial systems, administration of platelet activation inhibitors is established. In patients with TIPS implantation platelet activation inhibition appears to be a promising target, too. Altered platelet activation has been shown to be present in patients with liver cirrhosis. A platelet activating state can precisely be described in the portal venous system of cirrhotic patients. Portal hypertension
Fig. 3 Transplant-free survival by TIPS indication after PSM. a Transplant-free survival 12 months after TIPS-placement among patients with refractory ascites as TIPS indication was 89.6% in the PSM-aspirin-cohort and 70.6% in the PSM-no-aspirin-cohort (Kaplan–Meier curve, \( p < 0.001 \), log-rank test). b Transplant-free survival 12 months after TIPS-placement among patients with variceal bleeding as TIPS indication was 91.1% in the PSM-aspirin-cohort and 92.2% in the PSM-no-aspirin-cohort (Kaplan–Meier curve, \( p = 0.797 \), log-rank test). + , censored patients.
facilitates bacterial translocation and increases oxidative stress. Subsequently, several increased markers of platelet activation create a possibly prothrombotic environment as shown in the portal venous blood of patients undergoing TIPS implantation [26].

The effect of aspirin on patients after TIPS implantation has been studied before in a small prospective study \((n=44)\) in the era of bare-metal stents. At that time, no significant difference was found concerning shunt patency 3 months after TIPS placement. Importantly, 3-month administration of aspirin did not increase risk of rebleeding in this cohort consisting of almost 90% of patients receiving TIPS for recurrent variceal bleeding [27]. The same group later found beneficial effects of phenprocoumon (target INR 1.7–2.1) on shunt patency [20]. Periprocedural application of heparin was also shown to prevent shunt insufficiency [28]. PTFE-covering later improved prevention of development of pseudo-intimal hyperplasia and stent stenosis resulting in a much higher primary patency rate [13]. The discussed studies were performed before introduction of PTFE-stents and the results are not applicable on today’s patients.

Interestingly, transplant-free survival was only significantly improved in patients with refractory ascites as TIPS indication and not affected in patients with refractory variceal bleeding. It is known that patient with refractory ascites represent a cohort of more advanced cirrhosis [29]. Consequently, transplant-free survival after TIPS is also impaired in these patients compared to patients with variceal bleeding as indication for TIPS insertion and even differential cutoff values in prognostic-tools have been proposed [24]. In our study too, patients with variceal bleeding as TIPS indication show less advanced cirrhosis (see supplementary tables 2 and 3). Regardless of TIPS indication, aspirin did not improve survival significantly in patients with Child A cirrhosis. In addition, aspirin potentially increased the rate of rebleeding in those patients. Our study does not include data on adverse events of aspirin after TIPS placement to further investigate these hypotheses to explain the differential effect of aspirin after TIPS insertion. The lack of information concerning treatment adherence represents a further potential bias. The effects of other drugs with a positive influence on patient survival in cirrhotic patients (lactulose, statins, antibiotics etc.) have not been studied in this analysis as the respective data are unavailable. It is furthermore important to outline that the observed improvement of survival may not exclusively be due to effects of aspirin on the hepatic system. The higher number of censors in the PSM-aspirin-cohort possibly affects the results. Despite a statistically robust PSM-matching creating comparable patient cohorts according to aspirin use with no significant differences in baseline characteristics, an influence of the significant differences in the unmatched cohorts cannot be ruled out. In addition to possible imbalance of unknown and unmeasured confounders, this represents a major bias to our study in comparison to prospective randomized controlled trials [30].

Interestingly, the protective effect of aspirin on transplant-free survival occurs early after TIPS procedure. This may be explainable due the mortality being highest within the first 100 days after TIPS insertion specifically in patients with refractory ascites [31]. Causes of death were not analyzed separately in the presented study due to unavailability of data. However, application of aspirin implicates further potential beneficial effects in patients in liver cirrhosis after TIPS placement. In a cross-sectional analysis in patients with chronic liver disease, use of aspirin was associated with a lower index liver fibrosis [32]. In a prospective study, a beneficial effect of aspirin was confirmed as aspirin was associated with less severe liver injury in NAFLD and NASH and decreased risk of fibrosis progression [33]. In a nationwide study including all Swedish patients with viral hepatitis due to hepatitis B or hepatitis C infection, aspirin administration was even associated with a decreased liver-related mortality and decreased incidence of hepatocellular carcinoma without increasing the probability of gastrointestinal bleeding [34]. Clearly, these findings are individually insufficient to explain a superior survival already at 12 months after TIPS implantation as seen in our study. Information on TIPS shunt patency rates or recurrence rates of initial TIPS indications is lacking in our cohort. Thus, a beneficial effect of aspirin on the general disease progression in cirrhotic patients beyond direct effect concerning TIPS patency cannot be excluded. It is assumable that the beneficial effect of aspirin in TIPS patients results from a cumulation of the described effects on platelet activation, reduced progression of liver fibrosis and anticancerogenic effects. A longer follow-up period is needed to confirm these findings and a prospective study with detailed analysis of causes of death and adverse events is desirable.

The retrospective design of this study limits the reliability of its results. Due to the retrospective character of this study, patient-based differences in the decision whether aspirin was administered or not cannot be excluded. Despite well-balanced propensity score matching, confounding in treatment allocation may be underestimated in the matched cohorts. A selection bias of patients cannot be excluded. Heterogeneity of the respective patient cohort and medical regimen at the different institutions possibly affect the results.

In conclusion, this retrospective multicenter cohort study provides first evidence that aspirin administration after TIPS implantation has a substantial effect on transplant-free survival in patients with refractory ascites as TIPS indication. Our findings support the necessity for prospective randomized clinical trials to investigate the effects of aspirin in TIPS patients.
**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s12072-022-10330-x.

**Author contributions** Selected deidentified patient data will be shared upon valid request to the corresponding author. All the authors approved the final version of the article, including the authorship.

**Funding** Open Access funding enabled and organized by Projekt DEAL. Nothing to declare.

**Declarations**

**Conflict of interest** JT, speaking and consulting fees: Gore, Bayer, Alexion, MSD, Gilead, Intercept, Norgine, Grifols, Versantis, and Martin Pharmaceutical. DB: Consultant: Bayer Healthcare, Boston Scientific, Shionogi. Lectures: Falk Foundation. Leon Louis Seifert, Philipp Schindler, Lukas Sturm, Wenyi Gu, Quentin Edward Seifert, Jan Frederic Weller, Christian Jansen, Michael Praktiknjo, Carsten Meyer, Martin Schoster, Christian Wilms, Miriam Maschmeier, Hartmut H. Schmidt, Max Masthoff, Michael Köhler, Michael Schultheiss, Jan Patrick Huber, Dominik Bettinger, Jonel Trebicka, Moritz Wildgruber and Hauke Heinzw declare no conflict of interest.

**Ethical approval** The study was approved by the local ethics committee (2021-056f-S).

**Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

**References**

1. Tschochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. The Lancet 2014;383:1749–1761
2. Trebicka J. Emergency TIPS in a Child-Pugh B patient: when does the window of opportunity open and close? J Hepatol 2017;66:442–450
3. Trebicka J, Gu W, Ibáñez-Samaniego L, Hernández-Gea V, Pitarch C, García E, et al. Rebleeding and mortality risk are increased by ACLF but reduced by pre-emptive TIPS. J Hepatol 2020;66:442–450
4. Schultheiss M, Bettinger D, Thimme R, Rössle M. 30 Jahre transjugulärer intrahepatischer portosystemischer Shunt (TIPS)—Rückblick und Perspektive. Z Gastroenterol 2020;58:887–889
5. Rössle M, Ochs A, Gülberg V, Siegerstetter V, Holl J, Deibert P, et al. A Comparison of paraconsents and transjugular intrahepatic portosystemic shunting in patients with ascites. Engl J Med 2000;5:8
6. Bureau C, Thabut D, Oberti F, Dharancy S, Carbonell N, Bouvier A, et al. Transjugular intrahepatic portosystemic shunts with covered stents increase transplant-free survival of patients with cirrhosis and recurrent ascites. Gastroenterology 2017;152(157):163
7. Salerno F, Cammá C, Enea M, Rösöle M, Wong F. Transjugular intrahepatic portosystemic shunt for refractory ascites: a meta-analysis of individual patient data. Gastroenterology 2007;39:24
8. Deltenre P, Trêpo E, Rudler M, Monescillo A, Fraga M, Denys A, et al. Early transjugular intrahepatic portosystemic shunt in cirrhotic patients with acute variceal bleeding: a systematic review and meta-analysis of controlled trials. Eur J Gastroenterol Hepatol 2015;5:50
9. de Franchis R. Expanding consensus in portal hypertension. J Hepatol 2015;5:2
10. García-Pagán JC, Caka K, Bureau C, Lallement W, Appenrodt B, Luca A, et al. Early use of TIPS in patients with cirrhosis and variceal bleeding. N Engl J Med 2010;25:5
11. Boyer TD, Haskal ZI. The role of transjugular intrahepatic portosystemic shunt (TIPS) in the management of portal hypertension: update 2009. Hepatology 2010;25:56
12. Angeli P, Bernardi M, Villanueva C, Francoz C, Mookerjee RP, Trebicka J, et al. EASL clinical practice guidelines for the management of patients with decompensated cirrhosis. J Hepatol 2018;69:1207
13. Bureau C, Pagan JCG, Layrargues GP, Metivier S, Bellot P, Perreault P, et al. Patency of stents covered with polytetrafluoroethylene in patients treated by transjugular intrahepatic portosystemic shunts: long-term results of a randomized multicentre study. Liver Int 2007;27:742–747
14. Buechter M, Manka P, Gerken G, Canbay A, Blomeyer S, Wetter A, et al. Transjugular intrahepatic portosystemic shunt in patients with portal hypertension: patency depends on coverage and interventionalist’s experience. Dig Dis 2018;36:218–227
15. Nicoară-Farcău O, Han G, Rudler M, Angrisani D, Monescillo A, Torres F, et al. Effects of early placement of transjugular portosystemic shunts in patients with high-risk acute variceal bleeding: a meta-analysis of individual patient data. Gastroenterology 2021;2021:160
16. Barrio J, Ripoll C, Bafáres R, Echenagusia A, Catalina MV, Camuñez F, et al. Comparison of transjugular intrahepatic portosystemic shunt dysfunction in PTFE-covered stent-grafts versus bare stents. Eur J Radiol 2005;55:120–124
17. Cura M, Cura A, Suri R, El-Merhi F, Lopera J, Kroma G. Causes of TIPS dysfunction. Am J Roentgenol 2008;20:981–986
18. Stein CJ, Li H, Zhang J, Mayerle J, Ricke J, Gerbes AL, et al. Transjugular intrahepatic portosystemic shunt for patients with liver cirrhosis: survey evaluating indications, standardization of procedures and anticoagulation in 43 German hospitals. Eur J Gastroenterol Hepatol 2020;32:1179–1185
19. Siegerstetter V, Huber M, Ochs A, Blum HE, Rössle M. Platelet aggregation and platelet-derived growth factor inhibition for prevention of insufficientity of the transjugular intrahepatic portosystemic shunt: a randomized study comparing ticlopidine plus ticlopidine with heparin treatment. Hepatology 1999;29:33–38
20. Sauer P, Theilmann L, Herrmann S, Bruckner T, Roeren T, Richter G, et al. Phenprocoumon for prevention of shunt occlusion after transjugular intrahepatic portosystemic stent shunt: a randomized trial. Hepatology 1996;24:1433–1436
21. Patel SS, Guzman LA, Lin FP, Pence T, Reichman T, John B, et al. Utilization of aspirin and statin in management of coronary artery disease in patients with cirrhosis undergoing liver transplantation evaluation. Liver Transplant 2018;2018:24
22. Theoemmes FJ, Kim ES. A systematic review of propensity score methods in the Social sciences. Multivariate Behav Res 2011;46:90–118
23. Zakrison TL, Austin PC, McCredie VA. A systematic review of propensity score methods in the acute care surgery literature: avoiding the pitfalls and proposing a set of reporting guidelines. Eur J Trauma Emerg Surg 2018;44:385–395
24. Bettinger D, Sturm L, Pfaff L, Hahn F, Kloeckner R, Volkwein L, et al. Refining prediction of survival after TIPS with the novel Freiburg index of post-TIPS survival. J Hepatol 2021;74:1362–1372
25. NCT03005444. Anticoagulation for advanced cirrhotic patients after TIPS. https://clinicaltrials.gov/show/nct03005444. 2016
26. Queck A, Carnevale R, Uschner FE, Schierwagen R, Klein S, Jansen C, et al. Role of portal venous platelet activation in patients with decompensated cirrhosis and TIPS. Gut 2020;69:1535–1536
27. Theilmann L, Sauer P, Roeren T, Otto G, Arnold JC, Noeldge G, et al. Acetylsalicylic acid in the prevention of early stenosis and occlusion of transjugular intrahepatic portal-systemic stent shunts: a controlled study. Hepatology 1994;20:592–597
28. Siegerstetter V, Krause T, Rössle M, Haag K, Ochs A, Hauenstein KH, et al. Transjugular intrahepatic portosystemic shunt (tips): thrombogenicity in stents and its effect on shunt patency. Acta Radiol 1997;38:558–564
29. D’Amico G, Pasta L, Morabito A, D’Amico M, Caltagirone M, Malizia G, et al. Competing risks and prognostic stages of cirrhosis: a 25-year inception cohort study of 494 patients. Aliment Pharmacol Ther 2014;39:1180–1193
30. Nuttall GA, Houle TT. Liars, damn liars, and propensity scores. Anesthesiology 2008;108:3–4
31. Stockhoff L, Schultalbers M, Tergast TL, Hinrichs JB, Gerbel S, Meine TC, et al. Safety and feasibility of transjugular intrahepatic portosystemic shunt in elderly patients with liver cirrhosis and refractory ascites. PLoS ONE 2020;2020:15
32. Jiang ZG, Feldbrügge L, Tapper EB, Popov Y, Ghaziani T, Afdhal N, et al. Aspirin use is associated with lower indices of liver fibrosis among adults in the United States. Aliment Pharmacol Ther 2016;43:734–743
33. Simon TG, Henson J, Osganian S, Masia R, Chan AT, Chung RT, et al. Daily aspirin use associated with reduced risk for fibrosis progression in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2019;17:2776–2784
34. Simon TG, Duberg A-S, Aleman S, Chung RT, Chan AT, Ludvigsson JF. Association of aspirin with hepatocellular carcinoma and liver-related mortality. N Engl J Med 2020;382(1018):1028

Publisher’s Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.