World Journal of Pediatric Surgery

Increased morbidity associated with secondary abdominal closure in pediatric liver transplantation

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To cite: Costa CM, Fonseca EA, Pugliese R, *et al*. Increased morbidity associated with secondary abdominal closure in pediatric liver transplantation. *World J Pediatr Surg* 2025;**8**:e000975. doi:10.1136/wjps-2024-000975

Received 4 December 2024
Accepted 5 March 2025

ABSTRACT

Background The discrepancy in size between donor and recipient presents a complex challenge in pediatric liver transplantation (PLT), often necessitating secondary abdominal closure to prevent abdominal compartment syndrome. The aim of this study is to determine the variables associated with an increased risk of requiring secondary closure in PLT.

Methods The retrospective study analyzed all primary liver transplantations performed in patients under 18 years of age from January 2014 to July 2022. The primary endpoint was the risk of secondary abdominal closure. Variables analyzed included pretransplant status, perioperative and postoperative data.

Results A total of 664 PLT recipients were identified, of which 58 required secondary abdominal closure (8.7%). Most patients had biliary atresia (n=412, 62.0%), followed by metabolic diseases (n=78, 11.7%). Statistical difference were found in donor gender (p=0.020) and the recipient-to-donor body weight ratio (RDBW), which was lower in the secondary closure group (0.1±0.1 *vs.* 0.2±0.27; p=0.001), lower in secondary closure. The mean hospital and intensive care unit (ICU) stay after PLT was significantly longer in the intervention group compared to those with primary abdominal closure (24.4±20.4 days *vs.* 12.5±13.1 days, p<0.001). Multivariable Cox regression analysis identified male donor as an independent risk factor for secondary abdominal closure (hazard ratio 1.9, p=0.030).

Conclusions Patients requiring secondary closure were smaller, had a lower RDBW, and received grafts with a higher graft-to-recipient weight ratio (GRWR), Graft size modulation and secondary abdominal closure are currently the techniques used to prevent compartment syndrome in PLT, particularly for children with low body weight.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Secondary abdominal closure is a strategy used in pediatric liver transplantation to manage abdominal compartment syndrome, but its impact on morbidity remains unclear. Previous studies have highlighted concerns about infection and delayed recovery associated with open abdomen management.

WHAT THIS STUDY ADDS

⇒ Our study demonstrates that secondary abdominal closure in pediatric liver transplantation is associated with increased morbidity, including higher rates of infection and prolonged hospital stay. These findings suggest that the risks of this approach should be carefully weighed against its benefits.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study emphasizes the need for reevaluating current surgical strategies in pediatric liver transplantation. Surgeons should consider alternative closure techniques, such as graft size adjustment or optimized perioperative management to minimize complications. Further research is needed to refine best practices and improve patient outcomes.

INTRODUCTION

The size discrepancy between donors and recipients in pediatric liver transplantation (PLT) presents a multifaceted challenge. To prevent abdominal compartment syndrome, secondary abdominal closure has emerged as a safe and effective solution, particularly for smaller patients .[1] This technique mitigates increased abdominal pressure postoperatively, which can result from factors like excessive fluid replacement, portal vein clamping with intestinal edema, and swelling of the liver graft during ischemia-reperfusion injury.[2 3] Moreover, cases with graft-to-recipient weight ratio (GRWR) exceeding 4% and prolonged anteroposterior diameters pose additional complexities in managing abdominal closure.

Various techniques for secondary abdominal closure have been described, including the use of synthetic materials, mesh, biological acellular dermis derived from humans or pigs, and closure of the skin alone.[4–7] Despite these options aimed at alleviating abdominal tension postoperatively, their outcomes vary, and there is no consensus on the risk factors guiding their selection.

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This study aims to identify the risk factors associated with the need for secondary abdominal closure in PLT and evaluate the outcomes of patients undergoing this strategy.

METHODS

Study design and patients

This observational study used data acquired from a retrospective review of medical records and a prospectively collected database.

From January 2014 to July 2022, all primary liver transplantations performed in patients under 18 years of age at Hospital Sírio-Libanês and Hospital A. C. Camargo Cancer Center, in São Paulo, Brazil, were reviewed. Both living and deceased donors were included.

Procedures

The recipients were divided into two groups based on the method of abdominal closure following PLT. The control group comprised patients who underwent primary abdominal closure. The intervention group included patients who required secondary abdominal closure, defined as the use of alternative techniques to mitigate complications associated with large-for-size syndrome and abdominal compartment syndrome. In this group, abdominal closure on the day of transplantation was achieved using mesh (PROCEED, Ethicon, Edinburgh), skin-only closure, or the Bogotá technique. Pretransplantation and post-transplantation management, as well as the surgical procedures were provided by the same medical team at both hospitals. The preoperative evaluations, surgical techniques, and postoperative care for living donors were reported in previous publications.[8–10] Tacrolimus (FK 506, Prograf) and steroids were used for immunosuppression in most of the recipients. We used five types of graft in the sample: whole liver, left lobe, right lobe, left lateral segment (LLS) and reduced LLS grafts. Doppler ultrasound was done in the first postoperative day as needed, such as in cases of elevation in liver function tests following transplantation. Laboratory tests were taken daily until hospital discharge. Acute rejection was defined and graded as mild, moderate, or severe based on histopathologic findings by liver biopsy. Cultures were taken from patients with signs of infection, such as fever, tachycardia, or increased inflammatory laboratory tests (C-reactive protein, procalcitonin, white blood cell counts and differential), after PLT. These included blood cultures, surgical secretions cultures, and peritoneal fluid cultures .

Outcomes

The primary endpoint was the risk of secondary abdominal closure. Secondary outcomes included: recipient and graft survival, recipient hospital stay, recipient intensive care unit (ICU) stay and reoperation after transplantation, hepatic vein outflow obstruction, portal vein stenosis, late (>30 days) portal vein thrombosis (LPVT), early (≤30 days) portal vein thrombosis (EPVT), hepatic artery thrombosis (HAT), extrahepatic biliary stricture, and biliary leak.

Statistical analysis

Both cohorts were compared by analyzing the following recipient data: age, weight, *z*-score, presence of previous abdominal surgery, ascites, and pediatric end-stage liver disease (PELD) at transplant. The donor's age, sex, and body mass index (BMI), type of transplant, GRWR, ischemia time, and red cell transfusion at transplant were analyzed. The study performed a descriptive analysis of the postoperative progresssion of patients with secondary abdominal wall closure.

Numerical variables were summarized as mean±standard deviation (SD) or median (interquartile range, IQR). We used Student's *t*-test and Mann-Whitney test for normal and non-normal distributed data, respectively. We assessed the normality assumption by descriptive measures, normal plots, and Shapiro-Wilks' test. Categorical variables were expressed as numbers and percentage. Differences between groups were assessed using χ^2 or Fisher's exact tests.

We performed patient and graft survival analysis with the Kaplan-Meier product-limit estimates and compared patient subgroups using a two-sided log-rank test. A Cox regression analysis was performed to determine the variables independently associated with increased risk for secondary abdominal closure and for graft and patient loss. Variables that were significant at $p<0.10$ were selected for the multivariable analysis. We reported results from the final Cox multivariate model as hazard ratio (HR) and 95% confidence intervals (CI).

All analyses were performed using the Jamovi software (V.2.3.18) and R (V.4.2.2). A p value<0.05 was considered statistically significant.

RESULTS

A total of 664 PLT recipients were identified, of which 58 underwent secondary abdominal closure (8.7%). Most patients had biliary atresia (n=412, 62.0%), followed by metabolic diseases (n=78, 11.7%), Alagille syndrome (n=35, 5.3%), and malignancies (n=28, 4.2%). Table 1 shows a comparison of baseline characteristics between the two groups. Patients who underwent secondary abdominal closure were younger, more malnourished, with a higher PELD score, and weighed less than the control group. There were no significant differences in recipient gender, presence of ascites, or history of previous surgical procedures between the groups (table 1).

There were no statistically significant differences between groups in donor age or BMI. However, a statistical difference was observed in donor gender and a notable difference in the recipient-to-donor body weight ratio (RDBW), with the secondary closure group exhibiting lower RDBW ratio (0.1±0.1 *vs.* 0.2±0.27; p=0.001). Most patients had a living donor (n=623, 93.8%), and there

Table 1 Characteristics of recipients and donors

Characteristics	Primary closure (*n*=606)	Secondary closure (*n*=58)	*P* value
Recipient age (months)	39.9±50.3	15.0±27.2	<0.001
Recipient weight (g)	13.5±11.5	7.2±4.9	<0.001
Z-Score weight/age	−1.5±1.4	−2.2±1.4	<0.001
RPA	223 (36.8)	20 (34.4)	0.730
Ascites at PLT	321 (55.2)	39 (68.4)	0.056
PELD at PLT	13.2±12.3	19.5±9.1	<0.001
Donor age (year)	28.7±8.9	28.3±8.5	0.710
Donor gender, male	282 (46.6)	36 (62.0)	0.020
Donor BMI (kg/m^2)	23.6±3.3	24.1±3.6	0.270
RDBW	0.2±0.3	0.1±0.1	0.001
Living donor liver	566 (85.2)	57 (98.2)	0.140
Type of graft*			0.100
LLS	436 (78.6)	49 (86.0)	
LLS reduced	27 (4.9)	6 (10.5)	
LL	53 (9.6)	1 (1.8)	
RL	3 (0.5)	–	
Whole liver	36 (6.5)	1 (1.8)	
GRWR	3.2±1.6	4.5±1.3	<0.001
CIT (min)	47.3±37.3	51.6±34.5	0.410
RBC transfusion in PLT (mL/kg)	32.3±16.1	45±13.1	<0.001

Continuous variable was presented as mean±SD or median (IQR). Category variable was presented as *n* (%).

*Data was available for 57 patients in secondary closure group.
BMI, body mass index; CIT, cold ischemia time; GRWR, graft-to-recipient weight ratio; LL, left lobe; LLS, left lateral segment; PELD, pediatric end-stage liver disease; PLT, pediatric liver transplant; RBC, red blood cells; RDBW, recipient-to-donor body weight ratio; RL, right lobe; RPA, recipient previous abdominal surgery.

was no statistical difference between the groups in terms of the type of donor. In the secondary abdominal closure group, the following graft types were used: LLS (*n*=49, 86.0%), left lobe (*n*=1, 1.8%), whole liver (*n*=1, 1.8%), and reduced graft (*n*=6, 10.5%). There was no significant difference in graft reduction and primary closure of the abdominal wall between groups (*p*=0.130). The intervention group had a higher GRWR and received a higher red blood cell transfusion rate.

Secondary closure analysis

In the secondary closure group, only one patient initially underwent skin-only closure on the day of transplantation due to significant hemodynamic instability. In this case, abdominal packing and skin-only closure were performed as a temporary measure, with definitive abdominal closure using a mesh completed 12 days later during the same hospitalization. Most patients in this group (*n*=50, 87.7%) received mesh for abdominal wall closure. Among these, 39.4% required mesh removal due to reoperation, mesh extrusion, or signs of material infection. Approximately 11% of patients had acute kidney injury, and five recipients required renal replacement therapy. Most patients (85.6%) experienced some postoperative complication during their stay in hospital, and 36.2% required reoperation, of which 3.5% were reoperated due to complications of the mesh (infection or extrusion of the mesh). The primary reasons for surgical intervention were intestinal perforation (15.8%), followed by bleeding (10.5%) and intestinal obstruction (both 10.5%). Approximately one-third of recipients had positive cultures, including blood cultures (24.1%), surgical wound secretion cultures (5.1%), or abdominal fluids (5.1%). Half of the patients underwent liver biopsy, with an average of 2.3±1.6 procedures per patient (table 2). Biopsies showed cellular rejection in 70.6% of cases, most of which were acute and mild (41.7%). There was only one case of chronic rejection. 23 (39.6%) patients required readmission to the hospital within the first 12 months after PLT.

The multivariate Cox regression analysis identified the male donor (HR=1.9, 95% CI 1.0 to 3.5, *p*=0.030) as an independent factor associated with an increased risk of secondary abdominal closure in this cohort (table 3).

The mean hospital and ICU stay after PLT was longer in the intervention group compared with primary abdominal closure group (24.4±20.4 days *vs.* 12.5±13.1 days, *p*<0.001). There were no significant differences between

Table 2 Postoperative variables of the population with abdominal secondary closure

Variable	Secondary closure (*n*=58)
Intubation after PLT (days)	3.8±6.9
Peak AST in first week after PLT (g/L)	435.0 (277.0–666.0)
Peak ALT in first week after PLT (g/L)	545.0 (350.0–794.0)
Bilirubin on day 7 after PLT (mg/dL)	3.0±2.7
Bilirubin 12 months after PLT (mg/dL)	0.3±0.2
INR on day 7 after PLT	1.5±0.5
Acute kidney injury after PLT	6 (10.3)
Creatinine 12 months after PLT (mg/dL)	0.2±0.1
Any acute rejection after PLT	24 (70.6)
Grade of rejection	
Mild	10 (41.7)
Moderate	7 (29.2)
Severe	7 (29.2)
Positive culture after PLT	18 (31.0)
How abdominal closure was achieved*	
Suture closure with no artificial material	6 (10.5)
Use of mesh for closure	50 (87.7)
No closure at the end of follow-up	1 (1.8)
Follow-up (months)	43.8 (19.1–68.3)

Continuous variable was presented as mean±SD or median (IQR). Category variable was presented as *n* (%).
*Data were available for 57 patients.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; PLT, pediatric liver transplant.

Table 3 Cox regression analysis: risk of abdominal secondary closure

	HR	95%CI	*P* value
Recipient age (month)	1.00	0.98 to 1.02	0.950
Recipient BMI (kg/m^2)	0.91	076 to 109	0.300
Ascites at PLT (yes)	1.10	0.57 to 2.17	0.760
PELD at PLT	1.00	0.97 to 1.04	0.740
RDBW×100 (recipient/donor)	1.00	0.98 to 1.03	0.810
Donor gender (male)	1.94	1.06 to 3.56	0.030
GRWR	1.70	0.16 to 18.28	0.650
RBC transfusions at PLT(mL/kg)	0.70	0.07 to 7.43	0.770

BMI, body mass index; CI, confidence interval; GRWR, graft-to-recipient weight ratio; HR, hazard ratio; PELD, pediatric end-stage liver disease; PLT, pediatric liver transplant; RBC, red blood cells; RDBW, recipient-to-donor body weight ratio.

the groups in terms of EPVT, LPVT, HAT, biliary stricture, bile leak, or any reoperation after PLT. In the secondary abdominal closure group, there were no cases of retransplantation with a median follow-up of 3.7 years (table 4).

Patient and graft survival did not differ among the studied groups. One-year patient survival was 96.6% and 91.2% in the primary and secondary abdominal closure groups, respectively. At 60 months, patient survival was 90.2% in the primary closure group and 81.3% in the secondary closure group (figure 1). Graft survival at 12 months was 95.4% and 91.2%. At 60 months, it was 88.3% and 81.3%, respectively (figure 2).

DISCUSSION

Secondary abdominal closure is a critical strategy for reducing the risk of compartment syndrome in PLT recipients due to differences in dimensions between the graft and the recipient's abdominal cavity.[5] A variety of techniques are used in staged closure, ranging from simple skin closure initially, followed by posterior procedures focusing on fascial closure.[11] Commercially available prosthetic meshes are also employed, including synthetic options like silastic prosthetic closure[12] and GORE-TEX used in the Bogota technique, as well as composite materials such as PROCEED and biological alternatives like porcine acellular dermal matrix.[6] Moreover, there are reports of using cadaveric fascia from the same donor in deceased donor intestinal transplantation.[13]

Several factors contribute to increased abdominal pressure during the postoperative phase, including anteroposterior abdominal diameter, a high GRWR, prolonged portal vein clamping time resulting in intestinal edema, and ischemia-reperfusion injury to the graft.[3 14–16] Minimizing increases in abdominal pressure is crucial due to their negative impact on portal flow and the increased risk of vascular complications, especially those related to the portal vein.[17–19] Several medical centers use secondary abdominal closure as a preventive measure to manage rising intra-abdominal pressure.[3 5 20 21] In this study, patients who underwent secondary abdominal closure showed a higher GRWR, which aligns with findings in the existing literature. Notably, the lower RDBW in cases of secondary closure is an aspect that receives less emphasis in current literature but deserves recognition as a factor that might require the adoption of techniques to manage increases in abdominal pressure.[22] Patients with acute liver failure are at an increased risk of needing secondary abdominal closure.[23] While this study did not detect a significant association, the small percentage of patients who underwent transplantation during the study period due to acute liver failure (1.4%) may explain this outcome.

Many groups even advocate for secondary closure.[24–26] In the study by Schulze *et al*.,[26] the rate of silicon foil implantation for abdominal closure was 9 out of 23 cases (39%) in the large-for-size group (GRWR>4%).

Table 4 Secondary outcomes

Outcomes	Primary closure (*n*=606)	Secondary closure (*n*=58)	*P* value
Recipient hospital stay after PLT (days)	23±15.2	29.5±21.9	0.003
Recipient ICU stay after PLT (days)	12.5±13.1	20.4±20.4	<0.001
Any reoperation after PLT	108 (18.4)	19 (32.8)	0.009
Venous complication			
Late portal vein thrombosis	25 (4.1)	5 (8.6)	0.530
Early portal vein thrombosis	9 (2.3)	0 (0.0)	0.180
HVOO	1 (0.1)	0 (0.0)	0.670
Hepatic artery thrombosis	8 (1.4)	2 (3.5)	0.200
Extrahepatic biliary strictures	83 (14.1)	7 (12.3)	0.690
Bile leak after PLT	59 (10.0)	6 (10.5)	0.920

Continuous variable was presented as mean±SD and category variable was presented as *n* (%).
HVOO, hepatic venous outflow obstruction; ICU, intensive care unit; PLT, pediatric liver transplant.

Their series did not involve reductions in LLS, and final closure was achieved within 3–7 days. In our own experience, 33 out of 322 recipients (10.8%) with a body weight (BW) of 7 kg or less underwent staged abdominal closure. Indeed, in PLT for recipients with low body weight, there is no consensus on whether it is preferable to delay primary abdominal closure or to use monosegment/hyper-reduction of the graft.[18] The drawbacks of secondary closure include extended stays in the ICU and hospital, a heightened risk of wound infection and dehiscence, as supported by previous studies.[2 5 12] Additionally, the present study's findings also align with a high incidence (31%) of positive cultures post-transplantation with secondary closure. Conversely, hyper-reduction of the graft carries a higher risk of biliary fistula on the cut surface, increased bleeding risk, and longer surgical times.[27] Nevertheless, studies indicate that both approaches are safe.[20 23 28 29] To achieve optimal outcomes in this patient population, expertise in a range of techniques is essential.

Recently, to mitigate complications linked to secondary abdominal closure, our group has developed the anterior hepatic resection technique.[22] In the donor surgery, this anterior hepatic resection is performed in situ, with the cranial limit set 2 cm above the anteroposterior diameter, measured perpendicularly from the left bile duct to the liver surface. The cutting plane is maintained parallel to the liver surface, ensuring it remains above the Glisson's pedicle of segment IV. The anterior hepatic resection technique aims to achieve a GRWR of less than 4% while reducing the anteroposterior diameter of the LLS. In our initial experience, primary closure was successful in 7 out of 8 recipients, all of whom had an RDBW of less than 0.1, with all donors being male. Our updated data, as of March 2024 (unpublished), includes a total of 21 anterior hepatic resections in patients with an average BW of 6.4 kg. Except for one donor, all donors were male. Nearly all patients were successfully closed primarily, except for one from the original series. Our present study identified a male donor as the only risk factor for secondary closure (in multivariate analysis), consistent with most donors in the anterior hepatic resection series. Collectively, this information will assist transplant centers in better planning recipient operations. For instance, in LLS donation for small recipients (BW<7 kg), the combination of a male donor with a long LLS anteroposterior diameter (assessed via preoperative donor abdominal CT scan) and the recipient's low body weight may indicate the necessity for techniques such as graft size reduction, secondary closure, or both.

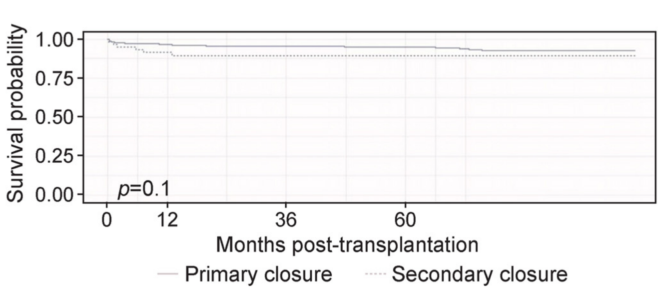

Figure 1 Kaplan-Meier survival curves: The dotted curve represents patients with secondary abdominal wall closure (*n*=58). The solid line represents the remaining patients with primary abdominal wall closure (*n*=606).

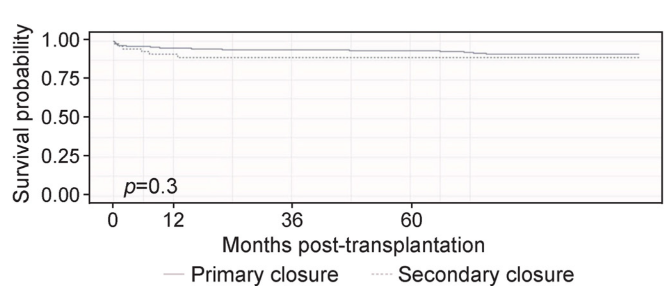

Figure 2 Kaplan-Meier graft survival curves: The dotted curve represents patients with secondary abdominal wall closure (*n*=58). The solid line represents the remaining patients with primary abdominal wall closure (*n*=606).

Patient and graft survival did not differ between groups, but those in the secondary abdominal closure group experienced higher rates of blood transfusion and reoperation, along with prolonged ICU and hospital stays. Consequently, the transplant procedure incurred increased costs. The added morbidity associated with secondary closure warrants careful evaluation by transplant teams, especially for low body weight patients. Our preliminary experience with anterior hepatic resection, which has been safe for both donors and recipients, has guided our transplant team towards graft size modulation. However, each team's experience will dictate the necessary interventions, sometimes requiring both secondary closure and graft size modulation.

This study has limitations inherent to retrospective and non-randomized data collection. Additionally, we were unable to perform a comparative analysis of all variables collected in the secondary abdominal closure group due to the small number of events in each modality. As a result, all types of secondary abdominal closure were grouped together.

In conclusion, very small patients present substantial challenges in PLT, highlighting the need to identify risk factors for secondary abdominal closure to enhance surgical planning. Our study found that patients requiring secondary closure were generally smaller, had lower RDBW, and received grafts with higher GRWR. These patients also faced higher rates of reoperation, increased need for blood transfusions, and extended ICU and hospital stays. Given these findings, adjusting graft size is a crucial strategy to reduce the need for secondary abdominal closure. Nonetheless, secondary abdominal closure itself remains a safe approach for preventing compartment syndrome in children with low body weight during transplantation.

Acknowledgements During the preparation of this work the author(s) used ChatGPT to improve language. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Contributors CMC contributes to the study design, data collection, analysis, writing, and review of the manuscript. EAF, RP, MRB, RV, NPTR, CMO, KR, and DPF contribute to the review of this manuscript. JSN contributes to the study design, data collection, analysis, writing, and review of the manuscript. JSN is the guarantor of this work and accepts full responsibility for the overall content, the integrity of the study, access to the data, and the decision to publish.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial, or not-for-profit sectors.

Competing interests The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Sirio-Libanes Hospital (HSL-2022-91). Consent for participation in the study was not obtained because this is a retrospective analysis based solely on medical record data. The Ethics Committee approved the waiver of the Informed Consent Form (ICF) due to the nature of the study and the absence of direct intervention with participants.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The data supporting this study are available from the corresponding author upon reasonable request.

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