Observation of Bleeding and MACCE Events in Patients with Liver Cirrhosis Complicated with Acute Coronary Syndrome after Antiplatelet Therapy

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ABSTRACT

Objective: To evaluate the efficacy and safety of dual antiplatelet therapy (DATP) in subjects with Child-pugh class A cirrhosis complicated with acute coronary syndrome (ACS) after coronary Drug-eluting stent (DES) implantation.

Study Design: Observational study.

Place and Duration of the Study: Department of Cardiology, Beijing You 'an Hospital, Capital Medical University, China, from January to August 2021.

Methodology: Cirrhotic patients with ACS after DES were divided into an early cirrhosis group (n=90) and a non-cirrhosis group (n=66). They underwent monthly follow-ups for 12 months, and DATP was administered with acetylsalicylic acid and clopidogrel in standard doses. The endpoints included efficacy endpoints (Major Adverse Cardiovascular and Cerebrovascular Events, MACCE) and safety endpoints (bleeding events). Endpoint events were calculated. Cox regression model and Kaplan-Meier survival curve were used to analyse the correlation between the two groups.

Results: The overall frequency of five indicators was higher in the early cirrhosis group, including increased heart rate (HR), abnormal renal function, abnormal liver function, thrombocytopenia, and coronary multivessel disease (84.5% *vs.* 51.6%, all $p<0.05$). Kaplan-Meier survival analysis showed no significant difference between early cirrhosis and non-cirrhosis groups ($p=0.688$ for MACCE, $p=0.960$ for bleeding events). Multivariate Cox regression analysis also showed no statistical difference between the early cirrhosis group and the non-cirrhosis group ($p=0.642$ for MACCE, $p=0.720$ for bleeding events).

Conclusion: In patients of ACS with early cirrhosis, 12 months of DAPT may be effectively and safely reduced MACCE after implantation of DES.

Key Words: *Acute coronary syndrome, Liver cirrhosis, Dual antiplatelet therapy, Major adverse cardiovascular and cerebrovascular events.*

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INTRODUCTION

Cirrhosis is chronic diffuse liver damage caused by long-term liver damage of different aetiologies. In 2017, there were 10.6 million patients with decompensated cirrhosis and 112 million patients with compensated cirrhosis worldwide.[1] There is no relevant report on the epidemiology of liver cirrhosis with coronary disease. The coagulation factors and platelets of patients with cirrhosis are low, and the prothrombin time and the international normalised ratio (INR) are prolonged. According to the past traditional concept, patients with liver cirrhosis are in a hypocoagulable state and are prone to bleeding, so, anticoagulation therapy is not recommended.

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However, in recent years, more and more studies have shown that coagulation factors and anticoagulation factors in patients with liver cirrhosis are reduced, and patients with liver cirrhosis are actually in a state of low coagulation, but this balance is extremely unstable and destroyed. If the balance is disturbed, the risk of bleeding and thrombosis increases.[2-4] DAPT, aspirin combined with P2Y12 receptor inhibitor is the basic therapy for preventing ischemic events after DES implantation. Current guidelines recommend that patients with ACS should take DAPT for at least 12 months, and patients with stable CHD should receive DAPT for 6 months. In patients with high ischemic risk, an extension to 30 months may be considered.[5,6]

Cirrhosis patients with ACS have a higher risk of thrombosis and bleeding, but the safety treatment of DATP is not clear. The PEGASUS TIMI 54 study enrolled 21,162 patients with stable CHD who had myocardial infarction in the past 1 to 3 years and 1 high-risk factor, and found that aspirin combined with ticagrelor can reduce the risk of MACCE in 3 years compared with aspirin alone, but significantly increase the risk of bleeding.[7]

The THEMIS PCI study enrolled 11,154 patients with stable CHD who received PCI and found that aspirin plus ticagrelor showed lower incidence of ischemic events and higher incidence of major bleeding than the aspirin alone group.[8] Clopidogrel has a lower incidence of bleeding events than ticagrelor.[9] It is worth investigating whether aspirin combined with clopidogrel antiplatelet therapy can reduce ischemic events without increasing bleeding events after coronary stent implantation in cirrhosis patients.

In clinical practice, the dose and duration of DAPT may be reduced in patients with CHD and cirrhosis.

The aim of this study was to investigate the safety and efficacy of DAPT with aspirin and clopidogrel for 12 months after coronary stent implantation in patients with liver cirrhosis.

METHODOLOGY

This study included patients attending Beijing You 'an Hospital affiliated to Capital Medical University, from August to September 2021. Inclusion criteria were ACS coexistent with liver cirrhosis, Child-pugh grade A with implantation of DES, and a follow-up time of 12 months. Exclusion criteria were eGFR <30 ml/min-1·1.73 m^2 or presence of hepatic failure. This study was approved by the Ethics Committee of Beijing You 'an Hospital, and all the selected patients signed an informed consent form.

The baseline clinical data of patients, including general clinical data, relevant laboratory indicators and coronary artery lesions, were collected through the electronic medical record system. General clinical data included demographic characteristics [body mass index (BMI)], systolic blood pressure (SBP), age, gender, heart rate (HR), estimated glomerular filtration rate (eGFR), smoking history, and drinking history, hypertension, history of diabetes, history of hyperlipidemia. Relevant laboratory indicators included liver function (ALT, AST), blood lipids (LDL-C, HDL-C), coagulation indicators (PT, APTT), and platelet count. Coronary artery lesions were obtained from coronary angiography images. Child-pugh and CRUSADE scores were calculated according to the standard scoring criteria.

Follow-up was conducted once a month after PCI for a total of 12 months. Telephone follow-up was conducted by an experienced researcher until September 1, 2022. Aspirin and clopidogrel use and endpoints were assessed at each visit.

Endpoints were MACCE and BARC type 2, 3, or 5 bleeding. MACCE was defined as a composite of all-cause death, nonfatal myocardial infarction, or stroke. Bleeding events were classified according to the BARC criteria.[10] All study endpoint events were investigated by the clinical events committee for data collection, centrally adjudicated and confirmed.

SPSS 20.0 software was used for statistical analysis. Shapiro-Wilk test (S-W Test) was used to check whether the data in each group conform to the normal distribution.

Normally distributed data were checked for mean ± standard deviation, and t-test was used for comparison between groups. Otherwise, the data were shown as M (Q1, Q3), and Mann-Whitney U test was used for comparison between groups. Enumeration data were expressed as frequency, and chi-square test was used for comparison between groups. Rates of end-point events (per 100 person-years) were calculated for the two groups of patients. Cumulative survival was performed using Kaplan-Meier survival curves and Log-rank test. Univariate and multivariate Cox regression models were used to analyse the association between cirrhosis and endpoint events. Multivariate Cox regression models were adjusted for statistically significant and clinically significant variables at baseline. Two-sided test was used, and $p<0.05$ was considered statistically significant.

RESULTS

One hundred and fifty-six patients with ACS aged 53.2±8.9 years were included. Out of them, 82 (52.6%) were males. Ninety patients were in the early liver cirrhosis group (57.7%) and 66 (42.3%) patients were in the non-cirrhotic group. There were no significant differences in age, gender, BMI, SBP, smoking, drinking, history of hypertension, diabetes, hyperlipidemia, blood lipid indexes, and coagulation indexes between the early cirrhosis group and the non-cirrhosis group (Table I). However, the early-stage liver cirrhosis group had a higher frequency of rapid HR, elevated eGFR, elevated ALT and AST, thrombocytopenia, and more coronary lesions ($p<0.05$).

Comparison of clinical prognosis: Follow-up time was 12 months, and 6 cases of MACCE occurred, including 4 cases in the early cirrhosis group and 2 cases in the non-cirrhosis group. Bleeding events occurred in 5 cases, including 3 cases in the early cirrhosis group and 2 cases in the non-cirrhosis group. The incidence of MACCE in the early cirrhosis group and the non-cirrhosis group were 4.44/100 person-years and 3.03/100 person-years, respectively, and the bleeding event rates were 3.33/100 person-years and 3.03/100 person-years, respectively. Kaplan-Meier survival analysis showed no statistical differences in cumulative survival analysis between the early cirrhosis group and the non-cirrhosis group ($p=0.688$ for MACCE, $p=0.960$ for bleeding events, Figure 1). Multivariate Cox regression analysis showed that there was no statistical difference between the two groups ($p=0.642$ for MACCE, $p=0.720$ for bleeding events, Figure 2).

DISCUSSION

Liver is an important organ of the human body. In addition to synthesising many important substances such as proteins required by the human body, it also plays an important role in the coagulation process. Liver can synthesise many coagulation factors and anticoagulation factors, which play an important role in maintaining the balance of the coagulation system. In cirrhosis patients, the synthesis of coagulation factors is reduced due to the massive destruction of liver cells. Hypersplenism due to cirrhosis leads to thrombocytopenia. Since patients with cirrhosis were previously considered to be in a hypocoagulable state, antithrombotic therapy is not recommended for patients with cirrhosis.

Table I: Baseline data and coronary lesions of the two groups of patients.

Project	Early-cirrhosis (n=90)	Non-cirrhosis (n=66)	Z/X^2	p-value/test name
Age, years	54.5 (45.8,57)	55 (45,58)	-0.329	0.742/Mann-Whitney U test
Male	47 (52.2%)	35 (53.0%)	0.01	0.92/chi-square test
BMI-Kg/m^3	25.3 (22.1,27.3)	25.2 (22.3,27.3)	-0.294	0.768/Mann-Whitney U test
SBP-mmHg	130 (114.8,143)	132 (114,143)	-0.034	0.973/Mann-Whitney U test
HR-bpm,	82 (68,89)	73 (65,83)	-3.879	<0.001/Mann-Whitney U test
eGFR <60 ml·min^{-1}·1.73 m^{-2}	11 (12.2%)	2 (3%)	4.212	0.04/chi-square test
Smoke	20 (22.2%)	18 (27.3%)	0.527	0.468/chi-square test
Drink	12 (13.3%)	16 (24.2%)	3.07	0.079/chi-square test
Hypertension	57 (63.3%)	46 (69.7%)	0.687	0.407/chi-square test
Diabetes	59 (65.6%)	41 (62.1%)	0.195	0.659/chi-square test
Hyperlipidemia	66 (73.3%)	48 (72.7%)	0.007	0.933/chi-square test
LDL-C-mmol/L	2.9 (2.1,3.1)	2.9(2.1,3.1)	-0.063	0.949/Mann-Whitney U test
HDL-C-mmol/L	0.9 (0.78,1.2)	0.9 (0.7,1.2)	-0.710	0.477/Mann-Whitney U test
ALT-U/L	30 (21,42)	22 (18.8,35)	-2.534	0.011/Mann-Whitney U test
AST-U/L	28 (18,41)	22 (18.8,35.8)	-1.194	0.232/Mann-Whitney U test
PT-sec	11.4 (10.9,13.6)	11.7 (10.9,13.7)	-0.209	0.835/Mann-Whitney U test
APTT-sec	30.3 (29.2,34.3)	30.2 (28.9,32.7)	-1.179	0.238/Mann-Whitney U test
PLT-*10^9/L	88 (71,121)	213 (176,239)	-8.128	<0.001/Mann-Whitney U test
Number of coronary lesions	2 (2,3)	2 (1,2)	-4.034	<0.001/Mann-Whitney U test

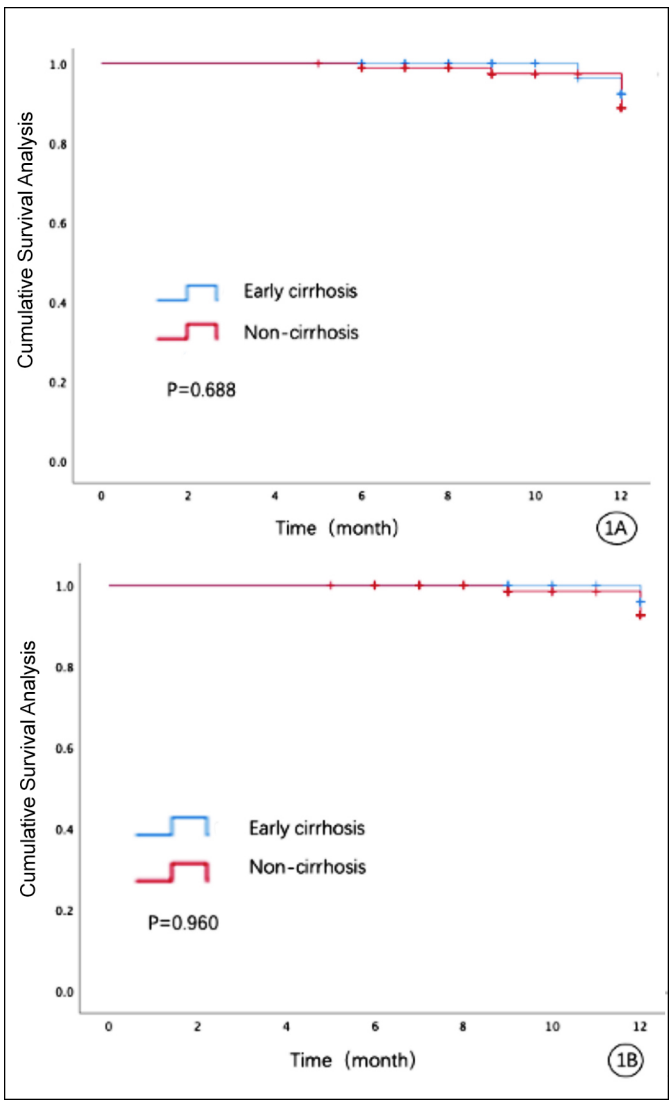

Figure 1: Kaplan-Meier survival analysis curve of end points of acute coronary syndrome patients in early cirrhosis group and non-cirrhosis group. (A) MACCE, (B) Bleeding.

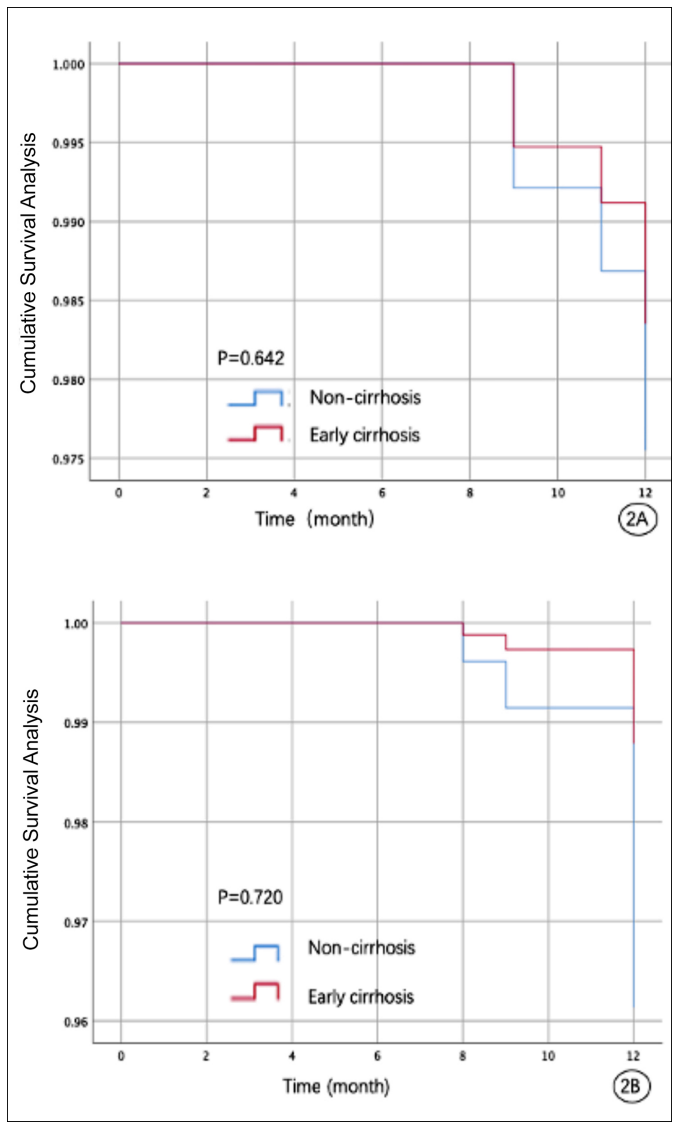

Figure 2: Multivariate Cox regression analysis of non-cirrhosis and early cirrhosis. (A) MACC, (B) Bleeding.

However, in recent years, more and more studies have shown that the synthesis of coagulation factors and anticoagulation factors in cirrhosis patients is reduced, and patients with liver cirrhosis can maintain a relative balance in a hypocoagulable state.[11] Liver cirrhosis leads to an increased risk of thrombosis, which may be due to vascular endothelial dysfunction leading to an increase in von Willebrand factor (vWF). This increase in vWF promotes platelet adhesion to the vascular endothelium and can reduce protein C and protein S levels, subsequently reducing the inactivation of coagulation factors.[12] Therefore, the antiplatelet therapy strategy for cirrhosis patients is not clear. This study prospectively collected clinical data of cirrhosis patients complicated by ACS, and analysed the safety and efficacy of antiplatelet therapy in patients with liver cirrhosis complicated by ACS. This study provides a clinical basis for antiplatelet therapy in cirrhosis patients who People suffering from ACS.

The baseline data of this study showed that the platelets in the early-stage cirrhosis population were significantly decreased because liver cirrhosis led to hypersplenism, which in turn led to the spleen phagocytosis and destruction of platelets, resulting in thrombocytopenia. Compared with the non-cirrhosis group, the heart rate in the early-stage liver cirrhosis group was faster, which may be due to the decreased detoxification ability of the liver caused by liver cirrhosis, the increase of toxins in the body, and the high circulation state caused by the retention of water and sodium, which caused the compensatory increase of the HR.

This study showed that in patients with early cirrhosis and ACS, after 12 months of DAPT with aspirin and clopidogrel after coronary stent implantation, the ischemic events and bleeding events were not significantly different from those in the non-cirrhotic group. The STOPDAPT-2 study, which included 3009 patients in 90 medical centres, found that 12 months of DAPT did not have a higher risk of bleeding than 1 month of DAPT.[13] Similar to the above study conclusions, this study showed that the incidence of bleeding events did not increase significantly with the prolongation of DAPT time in the early liver cirrhosis population, indicating that the application of DAPT may be safe in the early liver cirrhosis population. The TWILIGHT study is an international multicentre, prospective, randomised, and double-blind study. The 12-month bleeding event rate for DAPT in this study was 7.9%.[14] The GLOBAL LEADERS study included 15,839 subjects for a prospective study. The 12-month DAPT bleeding rate was 2.12%.[15] However, the present study showed that the 12-month DAPT bleeding rate in the early-stage liver cirrhosis population was 3.34%, and the difference in the bleeding rate between the two groups in this study (3.34% *vs.* 1.52%) was not statistical. Compared with the results of the two studies mentioned above, it is suggested that DAPT is safe in adequate doses in patients with liver cirrhosis. The mechanism may be that although coagulation factors are reduced in people with liver cirrhosis, their anticoagulant substances are also reduced, and the coagulation and anticoagulation mechanisms in patients with liver cirrhosis reach a low level of balance.[11] In patients with cirrhosis, coagulation factors and thrombocytopenia are reduced, and the coagulation and anticoagulant system is fragile and in a low-level balance, so the ability to form an effective embolism is low.[2-4]

Previous studies have shown that platelet adhesion and aggregation are reduced in patients with cirrhosis. Platelet membrane glycoprotein Ib (GP Ib) is decreased in patients with cirrhosis, which in turn results in a marked decrease in the platelet membrane glycoprotein Ib-IX-V complex. Because this complex is a receptor for VWF, it results in a significant reduction in VWF-mediated platelet adhesion. Fibrin degradation products inhibit the binding of fibrinogen to platelets, resulting in reduced platelet aggregation. In patients with liver cirrhosis, especially those with poor liver function, GMP-140 is significantly elevated, indicating that the platelets in patients with liver cirrhosis are in an activated state, so the risk of thrombosis increases.[16,17] This study found that patients with liver cirrhosis complicated with CHD were mostly multivessel lesions, and the lesions were more diffuse, which may be related to platelet activation in patients with liver cirrhosis. Although patients with cirrhosis have reduced platelet counts and reduced aggregation and adhesion, antiplatelet therapy is still necessary because platelets are in an activated state and have an increased risk of thrombosis. The ISAR-SAFE study included 4000 patients in 40 research centres in different countries. After 12 months of DAPT, the incidence of MACCE was 1.6%.[18] Similar to its results, the 12-month MACCE incidence of DATP in the non-cirrhotic population in this study was 1.52%. Although the 12-month DAPT MACCE incidence in the early-stage cirrhosis population was slightly higher (2.22% *vs*. 1.52%), the results of the two groups have no statistical difference. Thus, the risk of MACCE in the cirrhotic population was not reduced by thrombocytopenia. It may be the result of a combination of factors such as thrombocytopenia, decreased platelet aggregation, and platelet activation in people with cirrhosis. Therefore, antiplatelet therapy is necessary for this population. Because the ARCTIC study suggested that prolonging the DAPT time has no obvious benefit,[19] and liver cirrhosis itself is a high-risk group for bleeding, the DAPT time in this study was 12 months.

This study has a few limitations as it was an observational study. Although it can speculate on causality, the level of evidence is not as high as that of a randomised controlled study. The sample size was also limited. The study conclusions still need to be further verified by expanding the sample size.

CONCLUSION

The frequency of MACCE and bleeding in patients with early cirrhosis and ACS treated with DAPT for 12 months was not significantly different from that in the non-cirrhotic population. In such patients, 12 months of DAPT may be effective and safe.

ETHICAL APPROVAL:

This study was approved by the Ethics Committee of Beijing You 'an Hospital.

PATIENTS' CONSENT:
Informed consent was obtained from patients to publish the data concerning this study.

COMPETING INTEREST:
The authors declared no competing interest.

AUTHORS' CONTRIBUTION:
HC:Contributed to study design and data collection.
QS, HL, TT, JS: Contributed to data collection.
YL: Analysed and organised the data.
All the authors have approved the final version of the manuscript to be published.

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