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Research Article / Araştırma

The Relationship of Post-Operative FIB-4 Index Value with Morbidity and Early Mortality in Cardiac Surgery: A Retrospective Study

Kardiak Cerrahi Sonrası FIB-4 İndeks Değerinin Morbidite ve Erken Mortalite ile İlişkisi: Retrospektif Çalışma

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ABSTRACT

Objectives: Hepatic injury is seen in 10% of patients who underwent cardiopulmonary bypass (CPB). The fibrosis-4 (FIB-4) index is a non-invasive scoring method for detecting liver failure and liver fibrosis. We aimed to examine the effect of FIB-4 index value changes, which is measured in the early post-operative period, on morbidity and early mortality in cardiac surgery patients.

Methods: All patients had undergone elective coronary artery bypass graft surgery with standard sternotomy in the 2 years and were included in the study. In our study, the change in the pre- and post-operative period of the FIB-4 index, which was calculated in the pre-operative and post-operative period, was examined. Patients' demographic values, perioperative complications, amount of bleeding, total amount of fluid administered, and blood gas during cardiovascular bypass values were recorded.

Results: Patients were divided into two groups as those with FIB-4 index below 3.25 (Group 1) and above (Group 2). Group 1 consisted of 41 (27.2%) patients and Group 2 consisted of 110 (72.8%) patients. Although the mean time to intubate was higher in Group 2, no significant difference was found between the groups. The length of stay in the intensive care unit was significantly higher in Group 2 (p=0.033). When the 30-day mortality was compared, no difference was found between the groups (p=0.684).

ÖZ

Amaç: Kardiyopulmoner baypas yapılan hastaların %10'unda bir miktar karaciğer hasarı görülmektedir. Fibrozis-4 (FIB-4) indeksi, karaciğer yetmezliğini ve karaciğer fibrozunu saptamak için noninvaziv bir puanlama yöntemidir. Bu çalışmada, kalp cerrahisi hastalarında ameliyat sonrası erken dönemde ölçülen FIB-4 indeks değeri değişikliklerinin morbidite ve erken mortalite üzerine etkisinin incelenmesi amaçlandı.

Yöntem: Son iki yılda (2020-2021) standart sternotomi ile elektif koroner arter baypas greft cerrahisi geçiren 80 yaşın altındaki hastalar çalışmaya alındı. Çalışmada ameliyat öncesi ve ameliyat sonrası dönemde ölçülen FIB-4 indeksinin ameliyat öncesi ve ameliyat sonrası dönemdeki değişimi değerlendirildi. Hastaların demografik değerleri, perioperatif komplikasyonlar, kanama miktarı, verilen toplam sıvı miktarı ve kardiyovasküler baypas sırasındaki kan gazı değerleri kaydedildi.

Bulgular: Hastalar, FIB-4 indeksi 3,25'in altında (Grup 1) ve üstünde (Grup 2) olanlar olarak iki gruba ayrıldı. Grup 1 41 (%27,2) hastadan, grup 2 ise 110 (%72,8) hastadan oluşuyordu. Ortalama entübasyon süresi grup 2'de daha yüksek olmasına rağmen gruplar arasında anlamlı fark bulunmadı. Yoğun bakımda kalış süresi grup 2'de anlamlı olarak daha yüksekti (p=0,033). Otuz günlük mortalite karşılaştırıldığında gruplar arasında fark bulunmadı (p=0,684).

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Conclusion: It was observed that patients with high FIB-4 index have longer intensive care unit stay, which is an important morbidity criterion for cardiac surgery. We think that the post-operative period FIB-4 index may be effective in estimating morbidity in cardiac surgery patients.

Keywords: Cardiopulmonary bypass, FIB-4, fibrosis, hepatic failure, liver enzymes

Sonuç: Kalp cerrahisi için önemli bir morbidite kriteri olan FIB-4 indeksi yüksek olan hastaların yoğun bakımda kalış süresinin daha uzun olduğu görüldü. Kalp cerrahisi hastalarında morbiditeyi tahmin etmede postoperatif dönem FIB-4 indeksinin etkili olabileceğini düşünüyoruz.

Anahtar sözcükler: Fibrozis, fibrozis 4 indeksi, hepatik yetmezlik, kardiyopulmoner bypass, karaciğer enzimleri

Introduction

It is common to have a slight transient increase in liver function tests after cardiac surgery, and this increase peaks in the first 3 post-operative days. While the incidence of liver failure after cardiac surgery is 4%, some level of hepatic injury is seen in 10% of patients who underwent cardiopulmonary bypass (CPB).[1] Oxidative stress due to systemic inflammatory response syndrome and CPB may contribute to post-operative hepatic injury. In addition, decreased perfusion may cause centrilobular sinusoid ischemia and subsequent reperfusion injury. Medications given during and after surgery also contribute to hepatic injury.[2]

The fibrosis-4 (FIB-4) index is a non-invasive scoring method for detecting hepatic failure and hepatic fibrosis.[3,4] A FIB-4 index of <1.45 is mild, 1.45-3.25 is moderate, and >3.25 is classified as severe LV fibrosis.[5] Although the FIB-4 index has been used to detect level of hepatic fibrosis, especially in viral infections and non-alcoholic fatty liver disease, it has also been shown to be useful in predicting the prognosis of other liver diseases and cardiovascular- and liver-related mortality and morbidity with.[6] Although the effect of FIB-4 index on prognosis in patients with heart failure and atrial fibrillation has been examined, there is no study in the literature evaluating post-operative liver function with FIB-4 index after cardiac surgery.[7-9]

In our study, we aimed to investigate the effect of alterations in the FIB-4 index, which is measured in the early post-operative period, on morbidity and early mortality in coronary artery bypass graft surgery patients.

Methods

The study was carried out at Istanbul University-Cerrahpaşa, Institute of Cardiology after the approval of the Ethics Committee. All patients under the age of 80 who had undergone coronary artery bypass graft surgery under elective conditions with standard sternotomy in the past 2 years (2020-2021) were included in the study.

Patients underwent emergency surgeries, elderly patients (over 80 years of age), patients with a history of hepatic disease (viral hepatitis, acquired immunodeficiency syndrome, liver tumors, etc.), patients underwent off-pump surgery, patients who died during the perioperative period and patients underwent reoperation were excluded from the study.

The information of the patients was recorded by examining the hospital database, anesthesia follow-up form, perfusion follow-up form, and patient files.

Intervention and Anesthesia Regimen

The anesthesia procedure varied according to the preference of the anesthesiologist. However, induction was started with FiO_2=0.8 in all patients, as this is the standard practice in our clinic. By reducing the FiO_2 to 0.6, the tidal volume was ventilated under the pressure control mode of 6-8 ml/kg with a positive end-expiratory pressure of 3-5 cm/H_2O. Heparin was administered at a dose of 3-4 mg/kg by aiming the activated clotting time over 400 s and normothermic CPB with 100% oxygen was initiated. The blood flow was adjusted to be 2.4 L $min^{-1} \times m^2$ body surface area and the mean arterial pressure (MAP) was kept between 60 and 80 mmHg. Blood cardioplegia was performed at 20-min intervals on all patients. Blood gas was measured after each cardioplegia. Blood transfusion (erythrocyte suspension) was performed on the patients whose hematocrit level was below 20% during CPB and below 28% after CPB. All patients were taken to the intensive care unit and mechanical ventilation was performed. The patients were followed in the intensive care unit for at least 24 h.

Measurements and Clinical Information used in the Study

Patients' age, gender, chronic diseases, pre-operative ejection fraction (EF) values, pre-operative period hemogram and biochemistry measurements (ALT, AST, and Plt), operation time, cross clamp time, CPB duration, perioperative complications, amount of bleeding, total amount of fluid administered, and blood gas values during cardiovascular bypass were recorded. In the perioperative period, the MAP value was measured at the beginning and termination of the CPB and the lactate values in the blood gas measurements taken were recorded. Hemogram and biochemistry values of the patients in the post-operative period, EF percentage in echocardiography reports, extubation time (hours), intensive care unit stay (days), and 30-day mortality were recorded.

In our study, the change in the pre-operative and post-operative period of the FIB-4 index, which is calculated using ALT, AST, and platelet values measured in the pre-operative (within the past 1 week) and post-operative period (at the post-operative 24th h), was examined according to the formula: (FIB-4 index: (Age [years]×AST [IU/L])/(Platelet count [10^9/L]×√ALT [IU/L]).[5] We divided the patients into two groups as those with an FIB-4 index above 3.25, which is an indicator of severe liver fibrosis, and those without.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics for Windows, version 21.0 (Armonk, NY: IBM Corp.). All values are given as frequency (percent) and mean (standard deviation). The data were tested for normality using Kolmogorov-Smirnov and Shapiro-Wilk tests. Two independent groups were compared in the study. Pearson's Chi-square test or Fisher's exact test were performed to examine associations between categorical variables. For quantitative variables, the intergroup differences were compared using the independent-sample Student's t-test or Mann-Whitney test. All tests were two-sided. p values below 0.05 were considered statistically significant.

Results

By scanning the hospital database, 170 patients who underwent open heart surgery with the standard sternotomy method between 2020 and 2021 were identified. Of these patients, 151 were examined in the study and 45 (29.8%) of the patients were female and 106 (70.2%) were male (Fig. 1). The mean age of the patients was 59.62±9.47 years. The mean EF in the pre-operative echocardiography of the patients was 54.68±7.82%. The mean cross-clamp time and total CPB time were 100.07±38.31 min and 145.94±45.13 min, respectively. Total operation time was 281.5±76.98 min. The total amount of fluid administered during the operation was 3396.23±1065 mL and the total amount of bleeding was 785.1±299.32 mL. The mean time of intubation was 16.87±14.71 h. The mean MAP measured during CPB was 67.19±8.53 mmHg and the mean lactate value was 1.77±0.81. The mean length of stay in the intensive care unit was 3.55±2.74 days.

There were 100 patients (66.2%) whose FIB-4 index calculated in the pre-operative period was below 1.45 and the mean was 1.53±1.62. There were 4 patients (2.6%) with FIB-4 index calculated below 1.45 in the post-operative period, 36 patients (23.8%) between 1.45 and 3.25, and 111 (75.5%) patients with a FIB-4 index above 3.25, and the mean post-operative FIB-4 index of the patients was 6.21±4.7 (Table 1).

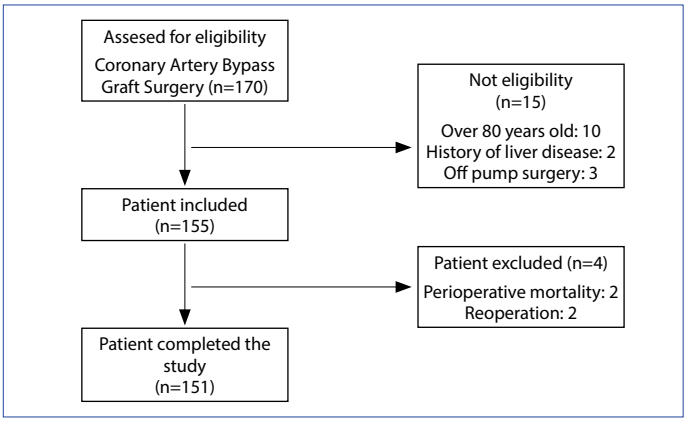

Figure 1. Flow chart of the cohort.

Patients were divided into two groups as those with FIB-4 index below 3.25 (Group 1) and above (Group 2). Group 1 consisted of 41 patients (27.2%) and Group 2 consisted of 110 patients (72.8%). The number of female patients in Group 2 was significantly higher than in Group 1 (p=0.022). In addition, the mean age of the patients in Group 2 was higher than in Group 1 (p=0.001). EF values and chronic disease rates were statistically similar between the groups (p>0.05). While ES use was significantly higher in Group 2 (p=0.006), no difference was observed between the groups when FFP and platelet use were compared (p>0.05). The total amount of bleeding during the operation was significantly higher in Group 2 than in Group 1 (p=0.015). On the other hand, while operative time and bypass time were similar between groups (p>0.05), cross-clamp period was significantly higher in Group 2 (p=0.012) (Table 2).

Although the mean time of intubation was higher in Group 2, no significant difference was found between the groups. The length of stay in the intensive care unit was significantly higher in Group 2 (p=0.033). When the 30-day mortality was compared, no difference was found between the groups (p=0.684) (Table 2).

Discussion

In our study, we examined the effect of cardiac surgery on liver function using the FIB-4 index. In the post-operative

Table 1. Comparison of liver enzymes and FIB-4 index of the groups

	Group 1 Mean±SD n %	Group 2 Mean±SD n %	p
Pre-operative FIB-4	1,21±0.54	1.65±1.87	0.075
Post-operative FIB-4	2.33±0.6	7.66±4.73	<0.001
FIB-4 Increase (%)	226.73±104.431	590.97±383.2	<0.001

FIB-4: The Fibrosis-4 index

Table 2. Comparison of the pre-, post-, and perioperative period findings of the groups

	Group 1			Group 2			p
	Mean±SD	n	%	Mean±SD	n	%	
Gender							
Female		6	14.6		39	35.5	0.022
Male		35	85.4		71	64.5	
Age (y)	55.80±7.73			61.05±9.69			0.001
Chronic diseases							
Hypertension		24	28.5		63	57.3	1
Diabetes mellitus		21	51.2		39	35.5	0.116
Dyslipidemia		8	19.5		15	13.6	0.523
Cerebrovascular accident		4	9.8		8	7.3	0.736
Atrial fibrillation		0	0		9	8.2	0.114
Myocardial infarction		9	22		14	12.7	0.251
Coronary stent		4	9.8		9	8.2	0.75
Perioperative period							
Erythrocyte suspension (Units)		24	58.5		90	81.8	0.006
Fresh frozen plasma (Units)		26	63.4		73	66.4	0.883
Platelet suspension (Units)		3	7.3		15	13.6	0.401
MAP (mmHg)	67.1±8.15			67.23±8.7			0.876
Lactate (mmol/L)	1.69±.66			1.8±0.86			0.599
Operation time (min)	266.4±58.77			287.12±82.28			0.103
Duration of CPB (min)	134.1±44.37			150.35±44.81			0.106
Cross-clamp duration (min)	86.53±36.03			105.12±38.07			0.012
Amount of bleeding (ml)	696.34±256.02			818.18±308.5			0.015
Fluid (ml)	3282.93±938.8			3438.45±1110.17			0.387
Post-operative period							
Duration of MV (Hours)	13.13±8.82			18.272±16.19			0.067
Duration of ICU stay (Days)	2.88±1.52			3.8±3.04			0.033
Mortality		1	2.4		7	6.4	0.684

FIB-4: The Fibrosis-4 index; MAP: Mean arterial pressure; CPB: Cardiopulmonary bypass; MV: Mechanical ventilation; ICU: Intensive care unit.

period, the number of patients with a FIB-4 index above 3.25, which is an indicator of severe hepatic damage, was quite high. It was observed that patients with a high FIB-4 index had more bleeding, more blood use, and longer intensive care unit stay.

Various studies have shown that hypoperfusion, free radical formation, oxidative stress, and increased catecholamine release during CPB plays a role in post-operative complications and organ dysfunction after cardiac surgery.[1,10] While most previous studies have focused on neurological, pulmonary, and renal complications, less attention has been paid to liver-related complications after cardiac surgery. However, it has been reported that approximately 10% of patients who underwent CPB experienced various degrees of hepatic damage.[1]

CPB causes increased physiological, immunological, and metabolic demands in the liver. The catecholamines released at the beginning of CPB reduce hepatic perfusion by 20% and hepatic arterial flow by up to 45%.[11] In studies comparing off-pump and on-pump surgery, it was shown that there was more hepatocellular damage in the patient group, in which, the CPB device was used.[12,13] This indicates the negative effect of the CPB device on hepatic function. On the other hand, in some controversial studies, CPB duration <2 h was not associated with impaired liver function tests.[14] In various studies, an increase in post-operative liver function tests has been found to be associated with the prolonged cross-clamp period.[13,15] In our study, it was observed that the cross-clamp period was significantly higher in patients with a high FIB-4 index. This shows the importance of surgical experience and speed to prevent post-operative complications due to cross-clamping.

Raman et al.[16] in their study, in which, they examined patients with severe ischemic early liver injury (SIELI) (post-operative ALT >500 IU/L) after cardiac surgery

showed that SIELI was significantly associated with low cardiac output and high load pressures and carried a high mortality risk. In the same study, heart failure, diabetes mellitus, hypertension, low cardiac output, and female gender were shown to be risk factors for SIELI. In our study, no relationship was found between chronic diseases and high FIB-4 index, but it was observed that female gender was associated with high post-operative FIB-4 index. Dong et al.[17] stated that old age is a risk factor for gastrointestinal complications, especially liver failure, after cardiac surgery with CPB. Similarly, patients who were older in our study had a significantly higher FIB-4 index. With this regard, it is important to state that female gender and old age are important risk factors for prognosis in major operations such as cardiac surgery.

Elevated liver enzymes are highly common after blood transfusion. Potential causes of the elevated liver enzymes after blood transfusion may be increased vascular permeability and ischemic hepatitis secondary to medications used after or concomitant blood transfusions medications.[18] The increase in the amount of perioperative bleeding and the FIB-4 index in our study can be explained by the higher rate of blood transfusion after bleeding.

In the study of Mihalopoulos et al.,[19] in which, they compared liver function over bilirubin levels in the early period after cardiac surgery, it was observed that patients with hepatic dysfunction had longer mechanical ventilation and intensive care unit stay, as well as a high mortality rate. In addition, in studies conducted with COVID-19 patients treated in hospital, it was observed that the FIB-4 index was associated with invasive ventilator need and mortality.[20,21] This showed that the FIB-4 index could be a prognostic indicator for different patient settings. In our study, the duration of mechanical ventilation was higher in Group 2, but it was not statistically significant. On the other hand, the length of stay in the intensive care unit was longer in patients with impaired hepatic function.

Limitations

Our study had some limitations. The important limitations were the retrospective nature of the study, the small number of patients, and the lack of long-term mortality follow-up. Although the study population was selected from patients without liver disease (liver USG, elastography, or liver biopsy that were not performed) and that is another important limitation. Another important limitation is that in addition to the FIB-4 index, other hepatic fibrosis scores such as aspartate aminotransferase-to-platelet ratio index, aminotransferase ratio to alanine, and Universal Index for Cirrhosis have not been studied.

Conclusion

Our study is very valuable in that it was the first study evaluating post-operative hepatic function in cardiac surgery patients using the FIB-4 index. In this study, it was shown that the amount of bleeding and blood transfusion in the perioperative period was associated with the FIB-4 index higher than 3.25, which indicates severe hepatic dysfunction in the post-operative period. In addition, female gender and age were found to be risk factors for increased post-operative FIB-4. It was observed that patients with high FIB-4 index had longer intensive care unit stay, which is an important morbidity criterion for cardiac surgery. We suggest that the post-operative period FIB-4 index may be effective in estimating morbidity in cardiac surgery patients.

Disclosures

Ethics Committee Approval: The study was approved by The Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine Ethics Committee (Date: 30/07/2021, No: 14935-A15).

Informed Consent: Written informed consent was obtained from all patients.

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