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Natural History and Risk Factors of the "Cholestatic Post-cardiac Surgery Syndrome"

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Abstract

***Objective*: To describe the natural history and risk factors of the cholestatic post-cardiac surgery syndrome.**

***Methods*: We reviewed all cases of patients with hyperbilirubinemia after cardiac surgery admitted to a large metropolitan referral hospital during January 2005 to December 2005 (n=317).**

***Results*: Fourteen patients (11 male, 3 female) developed postoperative hyperbilirubinemia after excluding hyperbilirubinemia secondary to acute cholecystitis, acute pancreatitis, and shock. Sixty four percent of patients have mild and subclinical hepatobiliary disease preoperatively. Preoperative echocardiography showed right ventricular enlargement and/or hypokinesis in most patients. The mean serum total bilirubin peaked at postoperative day 9 and return to normal by postoperative day 18. The highest recorded serum total bilirubin was 13 mg/dL (221 μmol/L). The mean serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) levels were mildly elevated and showed no distinct peak during postoperative period.**

***Conclusion*: In this series, 4.4% of patients undergoing cardiac surgery developed idiopathic post-operative jaundice. Preexisting liver disease and increased right heart pressures were associated with this syndrome. After excluding other causes of hyperbilirubinemia, serum total bilirubin can be expected to normalize in first 18 days after surgery.**

Key words: Cardiac surgery, hyperbilirubinemia, postoperative complication, hepatic congestion, jaundice, non-obstructive cholestasis.

Jaundice following cardiac surgery, frequently referred to as "post-pump jaundice," has been reported since the 1960's with an incidence of between 3 to 40% [1-8]. The incidence of jaundice following mitral valve replacement has been reported to be as high as 55% [1-5]. Jaundice following cardiac surgery has been associated with prolonged mechanical ventilation, prolonged intensive care unit (ICU) stay, and a higher mortality [1-6]. The causes of jaundice following cardiac surgery include acute cholecystitis, acute pancreatitis, shocked liver, and septic shock [2-4,9-12]. However, a subset of patients develop hepatic dysfunction without an obvious cause. Hepatic dysfunction in these patients is characterized by hyperbilirubinemia with a mild elevation in hepatic transaminases and no evidence of biliary obstruction on imaging [3]. This entity has been referred to as the "cholestatic post-cardiac surgery syndrome" [13]. The aim of this study was to examine the incidence, characteristics, natural history, and risk factors of

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this syndrome in the era of current cardiac surgery practice.

Patients and Methods

We retrospectively reviewed the records of 317 adult patients (all older than 18 years) who had been admitted to the cardiothoracic intensive care unit (CT-ICU) at Thomas Jefferson University Hospital during the period from January 2005 to December 2005 (bypass surgery n=220, valvular surgery n=90, orthotopic heart transplantation n=7). Thomas Jefferson University Hospital is a tertiary care 800 bed teaching hospital in central Philadelphia. This study was approved by our Institutional Review Board. The hospital chart and electronic medical records (LastWord 4.2.9, IDX systems Corporation, Burlington, VT) of the patients were reviewed. We abstracted data on all those patients who developed postoperative hyperbilirubinemia. For the purpose of this study, postoperative hyperbilirubinemia was defined as total bilirubin concentration over 2 mg/dL (34 μmol/L) within 14 days after surgery. Patients with pre-operative hyperbilirubinemia and those who had a definable cause of post-operative hyperbilirubinemia were excluded from this analysis.

The patients' de-identified clinical data were recorded in an electronic spreadsheet (Excel 2000; Microsoft; Richmond, WA). The data recorded included history of diabetes mellitus, liver disease, alcohol consumption and smoking, preoperative prothrombin time (PT; normal 11.5-14.9 s) and partial thromboplastin time (PTT; normal 23-33 s) off anticoagulation and serum B-type natriuretic peptide. Left ventricular ejection fraction, right ventricular size and function and estimated pulmonary artery systolic pressure were recorded from the preoperative echocardiograms. Total bilirubin (TB; normal 0.2-1.2 mg/dL [3.4-20.4 μmol/L]), direct bilirubin (DB; normal 0.0-0.4 mg/dL [0.0-6.8 μmol/L]), alanine aminotransferase (ALT; normal 1-45 IU/L), aspartate aminotransferase (AST; 7-42 IU/L), alkaline phosphatase (ALP; normal 25-120 IU/L), creatinine (normal 0.7-1.4 mg/dL [62-124 μmol/L]) and blood urea nitrogen (BUN; normal 10-26 mg/dL [3.6-9.2 mmol/L]) were recorded for postoperative days 0 to 18. The surgical factors recorded included the type of surgery, cardiopulmonary bypass time, cross clamp time and the number of units of packed red blood cells (PRBC) transfused in the postoperative period. Hemodynamic measurements recorded included cardiac output, cardiac index, central venous pressure, and pulmonary artery pressure at arrival to ICU, after 12 hours and after 24 hours. Summary statistics were compiled to allow a description of the patient population. Unless otherwise stated, all data are expressed as mean±SD. Trend data were plotted using Origin 7.5 (Northampton, MA).

Results

Postoperative hyperbilirubinemia was detected in 22 of the 317 (6.9 %) patients reviewed. Fourteen patients (4.4%) developed hyperbilirubinemia without an obvious cause and constituted the study population. Eight patients with secondary causes of hyperbilirubinemia were excluded from the study; three patients had acute cholecystitis that required laparoscopic cholecystectomy, one patient developed acute pancreatitis secondary to common bile duct stone and required endoscopic retrograde cholangiopancreatography and four patients were found to have hyperbilirubinemia due to shocked liver (n=3 cardiogenic shocks, n=1 septic shock).

The patients' demographic and clinical data are summarized in **Table 1** while their pre-operative echocardiographic and postoperative hemodynamic data are presented in **Table 2**. There were 11 male and 3 female patients; their mean age was 61 years (range 26 to 83 years). Six patients (42%) were diabetic, seven (50%) were smokers and six (42%) were moderate to heavy alcohol drinkers. Three patients underwent orthotopic heart transplantation; one for dilated cardiomyopathy and two for ischemic cardiomyopathy, four patients had coronary bypass graft (CABG) surgery, four patients had valve surgery, two patients underwent ventricular assist device placement for ischemic cardiomyopathy and one patient had CABG, valve surgery, and aortic root repair. Nine (64%) of the patients had preoperative evidence of hepatic disease,

which was asymptomatic in all the patients. The most common diagnosis was congestive hepatopathy (n=6) that was made based on clinical examination, liver function tests, and hepatic sonographic findings and in one case, transjugular liver biopsy (**Figure 1**). One patient each had chronic hepatitis C, chronic idiopathic hepatitis with mild activity and fatty liver diagnosed by liver biopsy. The mean preoperative PT and PTT (off anticoagulation) were mildly elevated at 15.6±1.6 s (normal 11.5-14.9 s) and 35.2±6.9 s (normal 23-33 s) respectively. B-type natriuretic peptide (BNP) which was measured in 7 patients ranged from 183 to 3033 pg/dL. The number of units of packed red blood cells (PRBC) transfused postoperatively ranged from 1 to 15 (mean of 8 units). The mean hospital stay was 29.6+20.4 days. Two patients died due to worsening heart failure. Preoperative echocardiography showed right ventricular enlargement and hypokinesia in 8 out of 13 patients (61.5%). Left ventricular ejection fraction ranged from 10% to 70%. Systolic pulmonary artery pressure (SPAP) was calculated echocardiographically in 9 patients, being greater than 35 mmHg in seven patients (77%). Measured pulmonary artery pressure was elevated in all patients in first 24 hours postoperatively; the CVP was 12.9±3.6 mmHg at time 0,11.6±2.6 at time 12 hours and 11.4±1.6 at 24 hours. The changes in TB, DB, AST, ALT, ALP, BUN and creatinine levels over post-operative days 1 to 18 are depicted in Figures 2- 4. Notably the mean serum TB level increased dramatically to a peak of 7.2 mg/dL (122 μmol/L) on post-operative day 9 returning to less than 2mg/dL (34 μmol/L) by post-operative day 18. The BUN and ALP increased slightly peaking at post-operative days 6 and 14 respectively before normalizing. The mean serum AST and ALT levels were mildly elevated with no distinct peak.

Discussion

In this study 14 of 317 (4.4%) patients undergoing cardiac surgery developed post-operative hyperbilirubinemia without an obvious primary cause (the cholestatic post-cardiac surgery syndrome). This incidence is similar to that of 3.2% reported by Michalopoulos and colleagues in a cohort of patients studied over a two year period from 1993 to 1995 [6]. The pattern of deranged liver function tests was similar in all our patients, with a dramatic increase in the total bilirubin (predominantly unconjugated) with mildly elevated ALP, AST and ALT. The increased total bilirubin was evident by day two, peaking on day 9 and returning to normal by post-operative day 18. This finding has been reported by other authors [1,3,13]. In the series by Wang *et al*, 70% of the increased total bilirubin was from an increase in unconjugated bilirubin [1]. However, in the series by Collins *et al*, Bøhmer *et al* and Michalopoulos *et al* most of the increase in bilirubin was conjugated [4,6,13].

Lockley and colleagues described centrilobular congestion and intrahepatic cholestasis in patients that developed jaundice following cardiac surgery [3]. In this series of patients liver necrosis was either absent or very mild. These authors demonstrated that the incidence of severe jaundice was higher in those patients with high right atrial pressures. Similarly, Bøhmer and colleagues demonstrated that patients whom developed jaundiced following cardiac surgery had higher preoperative right atrial and pulmonary artery pressures when compared to the non-jaundice patients [13]. Other studies have demonstrated that high preoperative right atrial pressures are associated with a higher risk hyperbilirubinemia after cardiac surgery [1,5]. In our case series all patients had elevated right atrial pressures in first 24 hours after surgery.

It is noteworthy that 64% of patients in our series had pre-operative hepatic dysfunction noted by either physical examination, imaging studies or liver biopsy. In addition a high percentage of patients had type two diabetes (increased risk for non-alcoholic steatosis) and were moderate to heavy consumers of alcohol. In our patients, the TB, PT and PTT were marginally increased at baseline. This suggests that subclinical liver disease may predispose patients to the cholestatic post-cardiac surgery syndrome.

The pattern of liver function abnormalities demonstrated in our patients and other series suggest increased unconjugated bilirubin levels as a result of hemolysis from cardio-pulmonary bypass and blood transfusions together with decreased hepatic capacity

for bilirubin disposal. While massive blood transfusion may increase the risk of post-operative jaundice the mean number of units transfused in our series was only eight. In the study by Collins *et al*, 20% of the patients who developed post-operative jaundice received five or fewer units of blood [4]. Chu and colleagues reported post-operative jaundice in 23.4% of 154 patients undergoing cardiac surgery [7]. In this, study right heart failure (raised right atrial pressure) and the amount of blood transfused were predictive of the development of jaundice [7]. Our patients had in common a predisposing constellation of clinical features which included pulmonary hypertension, right ventricular dysfunction and "asymptomatic" congestive hepatopathy. We suggest that acute hepatic congestion in the setting of chronic liver disease (mainly congestive hepatopathy) results a reversible defect of hepatic bilirubin excretion. The cholestatic post-cardiac surgery syndrome is distinguished from shock liver by the mildly abnormal transaminases and from obstructive causes of post-operative jaundice by a "normal" ultrasound examination. Post-operative sepsis may cause hepatocellular dysfunction with hyperbilirubinemia; however none of our patients were septic [2,3,13].

In conclusion, in our study 4.4% of patients developed non-obstructive cholestasis post cardiac surgery. Patients developed hyperbilirubinemia shortly after surgery with the bilirubin peaking on post-operative day 9 and returning to normal by day 18. Secondary causes of hepatobiliary disease were excluded. Preexisting liver disease and increased right heart pressures may contribute to the non-obstructive cholestatic syndrome.

Table 1. DEMOGRAPHIC AND CLINICAL DATA OF PATIENTS WITH POST OPERATIVE NON-OBSTRUCTIVE CHOLESTATIC SYNDROME

N	Age/ Sex	Type of surgery	CCT	BPT	Smoking	DM	Alcohol	Liver disease	PT (s)	PTT (s)	BNP	Units	Hospital stay	Outcome
1	83/F	MVR, AVR, TVR	184	223	+	+	-	Congestive hepatopathy	14.2	27	747	7	20	Alive
2	50/M	CABG	152	182	+	+	-	Hepatitis C	13	28	ND	6	33	Alive
3	71/M	CABG	80	97	+	-	+	Congestive hepatopathy	17.1	41	183	1	38	Alive
4	57/M	CABG	55	71	-	-	+	-	17.1	67	ND	5	9	Alive
5	66/M	CABG	0	0	+	+	+	Congestive hepatopathy	15.4	41	ND	7	11	Alive
6	57/M	MVR, TVR Modified Maze	197	245	+	-	+	Congestive hepatopathy	15.3	34	1313	7	42	Alive
7	62/M	Orthotopic heart transplant	-	-	-	-	-	Congestive hepatopathy	12.5	25	864	10	55	Alive
8	56/M	Orthotopic heart transplant	-	-	-	+	-	Chronic hepatitis	18.4	45	647	15	38	Alive
9	78/F	MVR, TVR	150	295	-	+	-	-	15.3	35	428	10	30	Alive
10	26/M	Orthotopic heart transplant	-	-	-	-	-	Congestive hepatopathy	18.3	30	3033	4	81	Alive
11	56/M	RVAD, LVAD	0	0	+	+	+	-	17.1	29	ND	14	18	Dead
12	59/M	CABG, AVR, aortic root repair	156	198	+	-	+	Fatty liver	14	30	ND	10	13	Alive
13	57/M	LVAD	0	0	-	-	+	-	17.1	29	ND	5	9	Dead
14	83/F	MVR	118	144	-	-	-	-	13.8	32	ND	12	18	Alive

AVR: Aortic valve replacement, BPT: Bypass time, BNP: B-type natriuretic peptide, CABG: Coronary artery bypass graft, CCT: Cross clamped time, F: Female, LVAD: Left ventricular assist device, M: Male, MVR: Mitral valve replacement, RVAD: Right ventricular assist device, TVR: Tricuspid valve repair.

Table 2. HEMODYNAMIC DATA OF PATIENTS WITH POST OPERATIVE NON-OBSTRUCTIVE CHOLESTATIC SYNDROME

Preoperative echocardiographic findings				Postoperative hemodynamic measurements (0- at arrival to ICU; 12- after 12 hours; 24- after 24 hours)								
N	LVEF (%)	Estimated SPAP (mmHg)	RV size and function	CVP-0 (mmHg)	CVP-12	CVP-24	PAP-0 (mmHg)	PAP-12	PAP-24	CI-0 (L/min/m^2)	CI-12	CI-24
1	55	80	Enlarged and hypokinetic	9	10	12	54/20	56/14	57/17	2.8	3.5	3.7
2	25	ND	Normal	14	10	7	33/16	30/20	26/16	-	3.7	4.6
3	70	29	Normal	14	15	6	38/23	34/22	26/16	2.7	2.6	2.8
4	35	ND	Normal	6	10	11	27/12	30/17	39/17	2.5	2.9	3.0
5	45	ND	Normal	9	8	12	38/21	44/19	44/22	1.6	2.3	2.2
6	40	38	Enlarged and hypokinetic	15	13	13	48/29	47/24	39/18	3.7	2.5	2.8
7	10	53	Enlarged and hypokinetic	10	14	12	38/20	33/20	27/15	2.6	2.5	2.7
8	10	38	Enlarged and hypokinetic	11	5	11	37/21	34/12	28/15	3.9	2.8	3.5
9	60	67	Enlarged and hypokinetic	11	16	12	39/19	50/26	54/22	2.3	2.0	2.4
10	10	46	Enlarged and hypokinetic	9	7	11	50/24	29/20	31/22	2.1	4.3	3.2
11	35	31	Enlarged and hypokinetic	27	12	10	60/30	31/18	34/25	1.4	-	-
12	25	ND	Normal	15	13	13	25/14	30/15	26/13	2.6	2.9	2.6
13	ND	ND	ND	19	22	17	-	-	31/22	-	-	-
14	35	68	Enlarged and hypokinetic	12	16	12	24/14	44/21	41/20	2.5	2.5	3.5

CI: Cardiac index, CVP: Central venous pressure, LVEF: Left ventricle ejection fraction, ND: Not done, PAP: Pulmonary arterial pressure, RV: Right ventricle, SPAP: Systolic pulmonary arterial pressure.

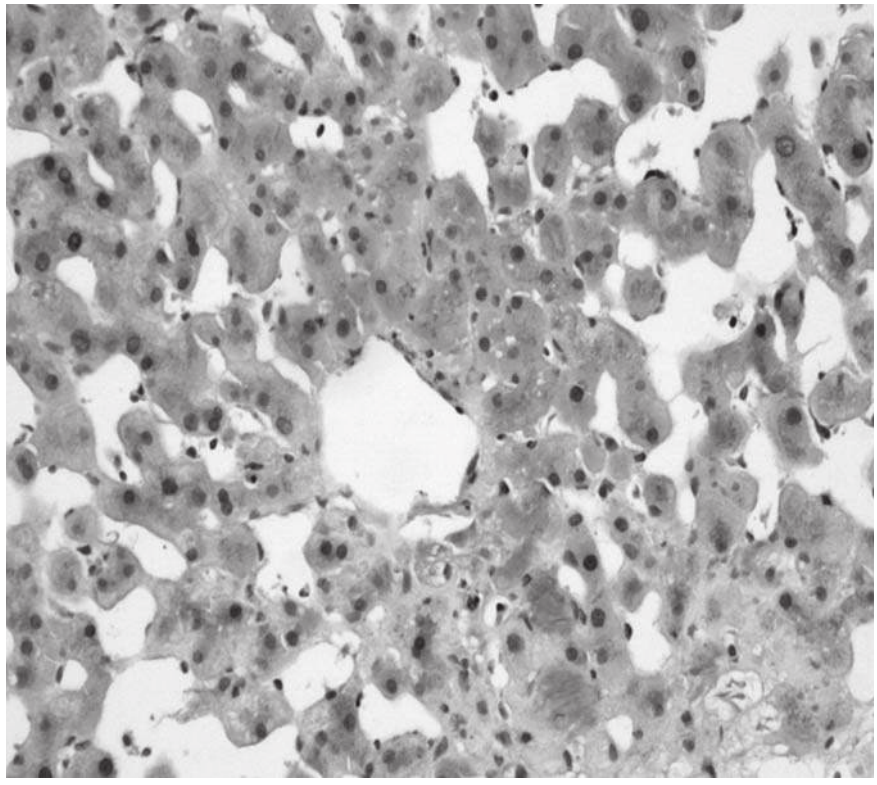


Figure 1. CHRONIC PASSIVE CONGESTION, CHARACTERIZED BY CENTRILOBULAR CONGESTION AND SINUSOIDAL DILATION (HEMATOXYLIN AND EOSIN STAIN, 200X)

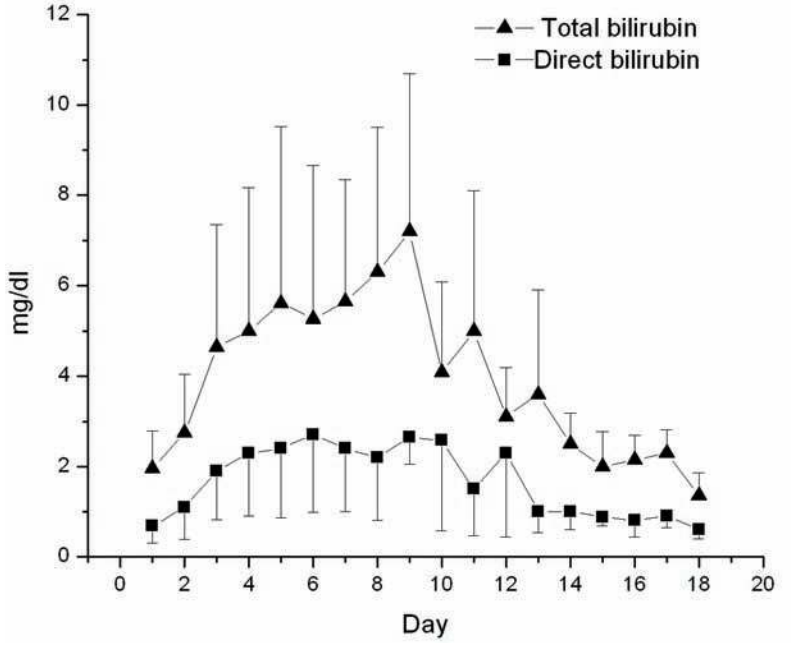
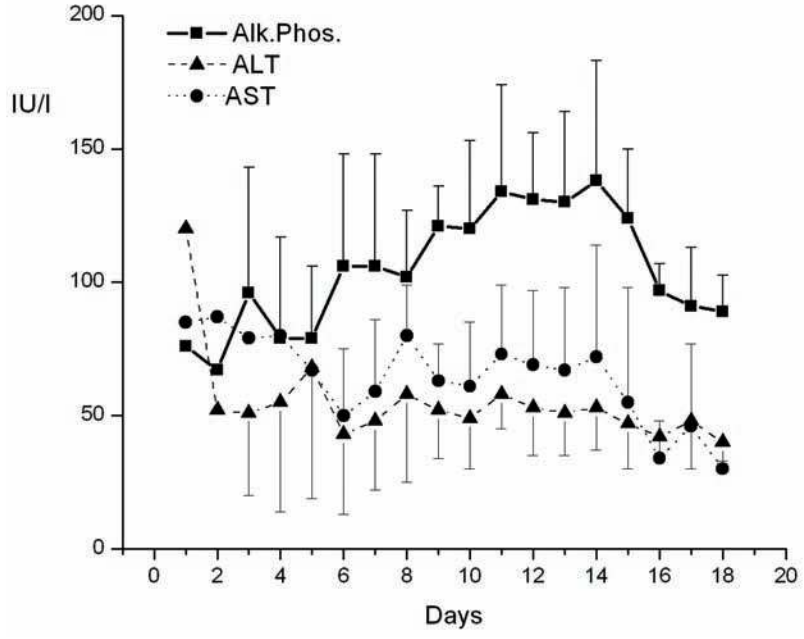


Figure 2. MEAN (AND SD) OF THE TOTAL BILIRUBIN AND DIRECT BILIRUBIN OVER THE POST-OPERATIVE COURSE

Figure3.MEAN(ANDSD)OFTHEALANINEAMINOTRANSFERASE (ALT), ASPARTATE AMINOTRANSFERASE (AST), ALKALINE PHOSPHATASE (ALP) OVER THE POST-OPERATIVE COURSE



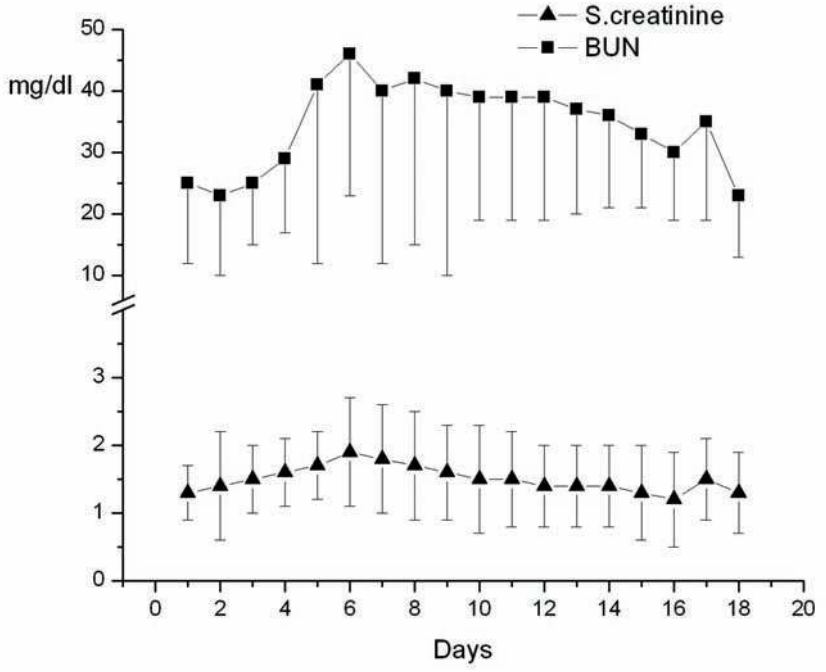


Figure 4. MEAN (AND SD) OF THE SERUM CREATININE AND BLOOD UREA NITROGEN (BUN) OVER THE POST-OPERATIVE COURSE

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