TITLE PAGE

Successful blood transfusion management of a living donor liver transplant recipient in the presence of anti-Jr^a: a case report

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Authors:
Nobuhiko Kurata[1]
Yasuharu Onishi[1]
Hideya Kamei[1]
Tomohide Hori[1]
Masahiko Komagome[1]
Chiaki Kato[2]
Tadashi Matsushita[2]
Yasuhiro Ogura[1]

Affiliations:
[1]Department of Transplantation Surgery, Nagoya University Hospital, Nagoya, Aichi, Japan
[2]Department of Blood Transfusion Service, Nagoya University Hospital, Nagoya, Aichi, Japan

Email addresses of authors:
kurata.nobuhiko@med.nagoya-u.ac.jp
onishiy@med.nagoya-u.ac.jp
kamei@med.nagoya-u.ac.jp
hori.tomohide@gmail.com
mkomagome@med.nagoya-u.ac.jp
ckato@med.nagoya-u.ac.jp
tmatsu@med.nagoya-u.ac.jp
oguchan@med.nagoya-u.ac.jp

Corresponding author: Yasuhiro Ogura, M.D., Ph.D.
Mailing address: Department of Transplantation Surgery, Nagoya University Hospital
65 Tsurumai-cho, Showa-ku, Nagoya, Aichi 466-8560, Japan
Tel: +81-52-744-2248
Fax: +81-52-744-1911
E-mail: oguchan@med.nagoya-u.ac.jp

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Abbreviations:
DSA, donor-specific antibody; HDNF, hemolytic disease of the newborn and fetus; HLA, human leukocyte antigen; LDLT, living donor liver transplantation; RBC, red blood cell

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Abstract

A 48-year-old Japanese woman was diagnosed with Budd-Chiari syndrome and transferred for possible living donor liver transplantation (LDLT). Examinations before LDLT revealed that the recipient had anti-Jr^a and pre-formed donor-specific anti-HLA antibodies (DSA). Rituximab was administrated at 16 days prior to the patient's scheduled LDLT for the prophylaxis of antibody-mediated rejection by DSA. The clinical significance of anti-Jr^a has not been clearly established because of the rarity of this antibody, so we discussed blood transfusion strategy with the Department of Blood Transfusion Service and prepared for Jr^a-negative packed RBCs. Intraoperative blood salvage was used during LDLT procedures to reduce the use of packed RBCs. Although post-transplant graft function was excellent, a total of 44 units of Jr^a-negative RBCs were transfused during the entire perioperative period. Because sufficient amounts of Jr^a-negative packed RBCs were supplied, Jr^a mismatched blood transfusion was avoided. The patient was discharged from our hospital on postoperative day 102 without clinical evidence of any blood transfusion related adverse events.

Although there are some controversies of blood transfusion related to anti-Jr^a antibodies, the current strategies of blood transfusion for liver transplantation with anti-Jr^a are i) sufficient supply and transfusion of Jr^a-negative matched packed RBCs and ii) application of intraoperative blood salvage to reduce the total amount of rare blood type RBCs. These strategies may be changed when the mechanism of anti-Jr^a alloimmunization is fully understood in future.

word counts: 228

Background

Jr^a is a red cell antigen that is highly prevalent in all populations. Rare Jr(a-) individuals can form anti-Jr^a antibodies after exposure to the Jr^a antigen through transfusion or pregnancy. Jr^a was first reported in 1970 by Stroup and MacIlroy who described five examples of the corresponding anti-Jr^a antibody in the Caucasian population [1]. Notably, the Japanese population has the highest frequency of the Jr(a-) phenotype [2]. However, even in the Japanese population, the prevalence of the Jr(a-) phenotype was estimated to be only 0.03–0.07% [3, 4]. Although a certain number of reports of anti-Jr^a have been described so far, the clinical significance of anti-Jr^a has not been clearly established.

In this report, we present a case of successful strategy and management for a living donor liver transplantation (LDLT) recipient with anti-Jr^a. The sufficient blood supply of Jr^a-negative red blood cells (RBCs) during the perioperative period and the application of intraoperative blood salvage during liver transplant procedure were the mandatory preparations in this particular setting.

Case Report

A 48-year-old Japanese woman visited a local hospital due to severe abdominal distension. As enhanced abdominal computed tomography demonstrated massive ascites and occlusion of the hepatic veins, she was diagnosed with Budd-Chiari syndrome. Although the elevation of liver enzymes was mild, she presented with uncontrollable massive ascites, severe hypoalbuminemia, and renal dysfunction. Since liver transplantation was indicated as a curative therapeutic option, she was transferred to our transplant center.

Her hepatic and renal profiles on admission were as follows: total bilirubin, 2.0 mg/dL; albumin, 2.2 g/dL; aspartate aminotransferase, 86 U/L; alanine aminotransferase, 133 U/L; prothrombin time-international normalized ratio, 1.33; and creatinine, 1.72 mg/dL. Her Child-Pugh score and Model for End-Stage Liver Disease score were 11 (grade C) and 23, respectively.

ABO/D blood typing of the recipient was Group AB, D positive. However, in RBC antibody-screening tests, her serum reacted weakly with all reagent RBCs. Further examination for irregular antibodies revealed the presence of anti-Jr^a antibody (antibody titer of 1:128 in Coombs test, 1:32 after dithiothreitol treatment for inactivation of IgM antibodies); and no other irregular antibodies were detected.

Before LDLT, blood transfusion strategy was discussed with the Department of Blood Transfusion Service (Table 1). Jr^a-negative packed RBCs should be used according to the guideline of the Japan Society of Transfusion Medicine and Cell Therapy [5]. Since the recipient's blood type was Group AB, she could receive Jr^a-negative packed RBCs of ABO-identical blood, or Jr^a-negative packed RBCs of compatible blood from any ABO blood types. Nonetheless, the supply of Jr^a-negative packed RBCs must be

limited, Jr^a-negative frozen thawed packed RBCs were also considered. In addition to the strategy of Jr^a matched allogeneic blood transfusion, we decided to introduce intraoperative blood salvage to reduce the use of Jr^a-negative packed RBCs during LDLT procedure. If Jr^a-negative packed RBCs and intraoperative blood salvage were running short during perioperative periods in spite of all these efforts, Jr^a-positive (incompatible) packed RBCs might be used for blood transfusion, which had a risk of disseminated intravascular coagulopathy.

Besides this concern of Jr^a irregular antibody, as we found moderate levels of pre-formed donor-specific antibodies (DSA) against donor class-I human leukocyte antigen (HLA) in this recipient, a total of 500mg of rituximab was administrated at 16 days prior to the patient's scheduled LDLT for prophylaxis of antibody-mediated rejection according to our protocol.

The living donor was her 20-year-old son. The ABO blood type combination was identical, but his Jr^a phenotype was Jr(a+), which was different from her Jr(a-). LDLT was performed using his left lobe graft, and the graft volume and graft recipient weight ratio were 442 g and 0.88%, respectively. The operative time was 12 hours 37 minutes. The total amount of collected fluid including both ascites and blood from the surgical field was 16,089 ml. The intraoperative blood salvage system collected 12,611 ml of bloody fluid, and processed 2,506 ml of washed packed RBCs, which was transfused to the patient in addition to 12 units of intraoperative allogeneic blood transfusion. There were no complications related to the usage of intraoperative blood salvage system. Tacrolimus, mycophenolate mofetil, and steroids were used for initial immunosuppression according to our pre-formed DSA LDLT immunosuppression protocol. She required many blood products for prolonged massive ascites and

hypoalbuminemia after LDLT. However, the post-transplant graft function was excellent. After the treatment of biliary complication, she was discharged from our hospital on postoperative day 102.

During her entire hospital stay, Jr^a-negative packed RBCs were prepared and transfused. Preoperatively, 8 units of ABO-identical Jr^a-negative packed RBCs and 4 units of ABO-identical Jr^a-negative frozen thawed packed RBCs were transfused. During LDLT, 4 units of ABO-identical Jr^a-negative packed RBCs and 8 units of ABO-compatible Jr^a-negative packed RBCs were transfused in addition to blood salvage. Postoperatively, 8 units of ABO-identical Jr^a-negative packed RBCs and 12 units of ABO-compatible Jr^a-negative packed RBCs were transfused when required (Table 2). Because Jr^a-negative packed RBCs were successfully provided during her hospital stay, there was no need of Jr^a-positive (incompatible) packed RBCs blood transfusion. Therefore, there was no clinical findings of acute intravascular hemolysis during the perioperative period. Her hemoglobin was 8.9 g/dL at the time of hospital discharge (Fig. 1).

The final anti-Jr^a titer obtained after all Jr^a-negative packed RBCs transfusion was 1:128 in Coombs test and 1:32 after dithiothreitol treatment, which were the same results as the preoperative titer. No other irregular antibodies against blood group antigens were identified.

Discussion

Among more than 300 known blood group antigens expressed on RBC, Jr^a is present on RBC at a very high frequency. Anti-Jr^a antibodies are generated through blood transfusion or pregnancy, and have never been described as naturally occurring antibodies. Because of the low incidence of this antibody, the clinical significance is not well established. To date, several case reports have described the presence of anti-Jr^a antibodies, primarily in pregnant women, highlighting their potential to cause hemolytic disease of the newborn and fetus (HDNF). Most cases of HDNF associated with anti-Jr^a are mild to moderate in intensity, and there is no need for treatment beyond phototherapy [6-8]. However, recent case reports have shown that anti-Jr^a antibodies have the potential for causing hydrops fetalis and severe anemia [9], and a fatal case of HDFN [10], suggesting that the roles of anti-Jr^a antibodies alloimmunization should be taken into account seriously.

In the setting of Jr^a incompatible blood transfusion, no biological or clinical evidence of hemolysis to mild acute or delayed transfusion reactions have been reported for anti-Jr^a antibodies. Yuan et al. [11] reported a case of a 32-year-old woman with a previously identified anti-Jr^a antibody who required massive transfusion of RBCs after developing life-threatening postpartum disseminated intravascular coagulopathy. Despite the emergent transfusion of 15 units of Jr^a untested RBCs, she did not develop laboratory or clinical evidence of acute hemolysis. Her anti-Jr^a titer increased 4-fold from a pretransfusion titer of 1:4 to 1:64 on day 10 post-transfusion. Her hematocrit was stable at 36.8% on day 27 post-transfusion. In contrast, Kwon et al. [12] reported a case of an acute hemolytic transfusion reaction due to anti-Jr^a antibodies in the context of repeated exposure to the Jr^a antigen. Although the patient was initially transfused with 2 units of

Jr^a-positive packed RBCs without any clinical evidence of hemolysis, she developed signs and symptoms of an acute hemolytic transfusion reaction 6 hours after additional 1 unit of Jr^a-positive packed RBC transfusion.

Several studies have been performed to assess the clinical significance of anti-Jr^a antibodies. Using a ^{51}Cr RBC survival test, Kendall reported the moderately rapid destruction of RBCs in a patient with an incompatible Jr(a-) phenotype with anti-Jr^a antibodies, arguing that anti-Jr^a may be a clinically significant antibody [13]. The monocyte monolayer assay has also been used in some studies of high-frequency antigens, where reactivity greater than 5% indicates potential clinical significance [14]. However, the specific mechanisms of anti-Jr^a antibody toxicity remain unclear.

In this reported case, rituximab was administered prior to LDLT. Rituximab, a chimeric anti-CD20 monoclonal antibody, has been widely used for desensitization in ABO- and HLA-incompatible solid organ transplantation [15, 16]. The treatment leads to B-cell depletion and has significant benefits in the prevention of antibody-mediated rejection [17]. In our case, DSA as well as anti-HLA antibodies were decreased after administration of rituximab and immunosuppressive agents (data not shown). Interestingly, there were no changes in the level of anti-Jr^a antibody titers before and after rituximab administration or liver transplantation. These results suggested that rituximab may not have the ability to inhibit the production of anti-Jr^a antibodies, and may not be useful for desensitization of anti-Jr^a, which was different from the desensitization of ABO- or HLA-incompatible transplantation.

Most transfusions of Jr^a-positive RBCs will not result in significant acute or delayed hemolysis in the presence of anti-Jr^a antibodies [6-8, 11]. However, the low incidence of the Jr(a-) phenotype may cause an underestimation of the risk of Jr^a alloimmunization

131 [9-10, 12]. Because anti-Jr^a antibodies can cause significant acute hemolysis in some
132 cases after repeated exposure to Jr^a-positive RBCs, attempts to locate Jr^a-negative RBC
133 units are warranted when anti-Jr^a antibodies are identified.
134 Our perioperative strategy for anti-Jr^a antibodies was determined prior to LDLT.
135 Preparation of Jr^a-negative packed RBCs was mandatory in cooperation with in-hospital
136 Blood Transfusion Service and the Japanese Red Cross Society. Because the supply of
137 Jr^a-negative packed RBCs was limited, intraoperative blood salvage was utilized to
138 reduce allogeneic blood transfusion during operation. With this strategy, there was no
139 trouble related blood transfusion in this recipient, and she could avoid hemolytic
140 transfusion reaction because of the no use of Jr^a mismatched blood transfusion.

Conclusions

Although there are some controversies of blood transfusion related to anti-Jr^a antibodies, we believe our strategy of anti-Jr^a antibodies is the current solutions: i.e. i) preparation and blood transfusion of Jr^a-negative matched packed RBCs to avoid the unsure use of anti-Jr^a incompatible RBCs, and ii) application of intraoperative blood salvage to reduce the rare blood type RBCs supply problem. Future strategy for anti-Jr^a may be changed when the mechanism of anti-Jr^a alloimmunization is fully understood.

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198 **Figure Legends**

199 **Figure 1: Clinical course of the liver transplant recipient.** The recipient required
200 frequent blood transfusions of Jr^a-negative packed RBCs before and after LDLT. The
201 post-transplant graft function was excellent, and the recipient was discharged from our
202 hospital on postoperative day 102. Abbreviations: Hgb, hemoglobin; RBC, red blood
203 cell; LDLT, living donor liver transplantation; AST, aspartate aminotransferase; ALT,
204 alanine aminotransferase; T-bil, total bilirubin

205

Table 1: Our perioperative strategy of blood transfusion for the liver transplant recipient with anti-Jr[a]

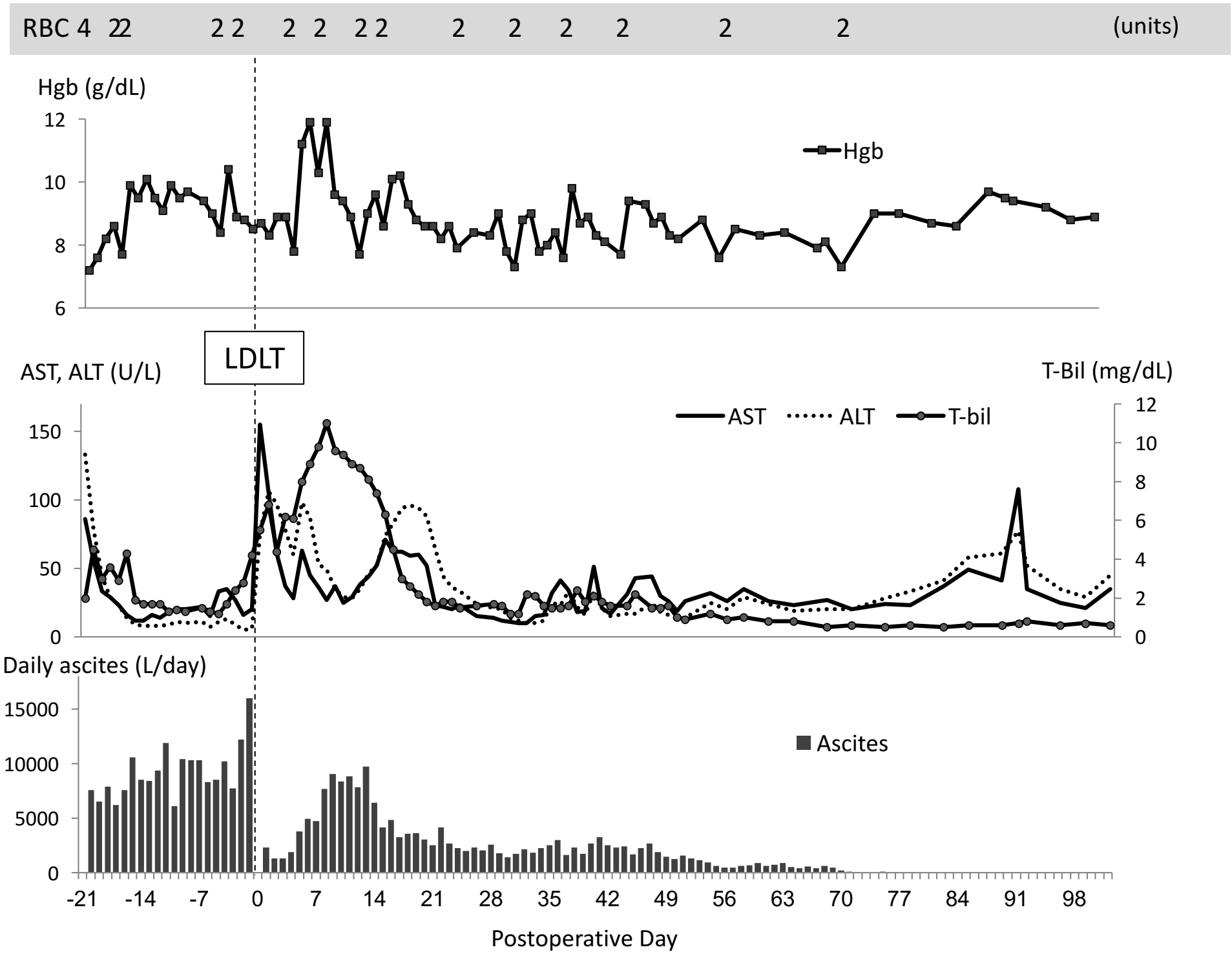
Types of blood transfusion	Strategy
Allogeneic blood transfusion	Selection sequence
	1. ABO-identical, Jr(a-) RBCs
	2. ABO-compatible, Jr(a-) RBCs
	3. ABO-identical, Jr(a-) frozen thawed RBCs
	4. ABO-compatible, Jr(a-) frozen thawed RBCs
	5. ABO-identical, Jr(a+) incompatible RBCs
	6. ABO-compatible, Jr(a+) incompatible RBCs
Autologous blood transfusion	Intraoperative blood salvage during LDLT

RBC red blood cell, *LDLT* living donor liver transplantation

Table 2: Units of transfused Jr^a-negative packed RBCs during the perioperative periods

Periods	ABO-identical Jr(a-) RBCs (units)	ABO-compatible Jr(a-) RBCs (units)	ABO-identical Jr(a-) frozen thawed RBCs (units)
Pre-operative	8	-	4
During LDLT	4	8	-
Post-operative	8	12	-

RBC red blood cell, *LDLT* living donor liver transplantation


RBC 4 2 2 2 2 2 2 2 2 2 2 2 2 2 2 (units)
Hgb (g/dL)
12
10
8
6
Hgb
LDLT
AST, ALT (U/L)
T-Bil (mg/dL)
150
100
50
0
AST
ALT
T-bil
12
10
8
6
4
2
0
Daily ascites (L/day)
15000
10000
5000
0
Ascites
-21
-14
-7
0
7
14
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49
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Postoperative Day