Low Preoperative Antithrombin III level is Associated with Postoperative Acute Kidney Injury after Liver Transplantation

Kyoung-Sun Kim
Asan Medical Center,University of Ulsan College of Medicine
Young-Jin Moon
Asan Medical Center, University of Ulsan College of Medicine
Sung-Hoon Kim
Asan Medical Center, University of Ulsan College of Medicine
In-Gu Jun
Asan Medical Center, University of Ulsan College of Medicine
Hye-Mee Kwon
Asan Medical Center, University of Ulsan College of Medicine
Jun-Gol Song (jungol.song@amc.seoul.kr)
Asan Medical Center, University of Ulsan College of Medicine https://orcid.org/0000-0002-6076-6978
Gyu-Sam Hwang
Asan Medical Center, University of Ulsan College of Medicine

Research

Keywords: Acute kidney injury, Antithrombin, Liver transplantation

Posted Date: March 1st, 2021

DOI: https://doi.org/10.21203/rs.3.rs-259177/v1

Abstract

Background: The reno-protective effect of Antithrombin III (ATIII) has been well-studied in various animal studies; however, little is known about the effect of ATIII on kidney function in patients undergoing liver transplantation (LT). This study aimed to determine the association between preoperative ATIII level and postoperative acute kidney injury (AKI) after LT (post-LT AKI).

Methods: We retrospectively evaluated 2,395 LT recipients between 2010 and 2018 whose data of perioperative ATIII levels were available. Patients were divided into two groups based on the preoperative level of ATIII (ATIII<50% vs. ATIII≥50%). Multivariable regression analysis was performed to assess the risk factors for post-LT AKI. In addition, subgroup analysis for the Model for End-stage liver disease (MELD) score (<20, ≥20) and donor types (deceased vs. living) were performed to identify the predictive value of ATIII.

Results: The mean preoperative ATIII levels were 30.2±11.8% in the ATIII<50% group and 67.2±13.2% in the ATIII≥50% group. The incidence of post-LT AKI was significantly lower in ATIII≥50% group compared to that in the ATIII<50% group (54.7% vs. 75.5%, *P*<0.001; odds ratio [OR, per 10% increase of ATIII level] 0.86, 95% confidence interval [CI] 0.81–0.92; *P*<0.001). The prognostic value of ATIII was found to be statistically significant in the low-MELD group (<20, OR 0.82, 95% CI 0.77–0.87, *P*<0.001) and living donor LT (OR 0.89, CI 0.85–0.94, *P*<0.001) group. After a backward stepwise regression model, female sex, high body mass index, low albumin, deceased donor LT, longer duration of surgery, and high red blood cell transfusion remained significantly associated with post-LT AKI.

Conclusion: Low preoperative ATIII level is associated with post-LT AKI, suggesting that preoperative ATIII might be a prognostic factor for predicting post-LT AKI.

Background

Acute kidney injury (AKI) after liver transplantation (LT) (post-LT AKI) is common and has an adverse impact on graft survival and mortality [1, 2]. Furthermore, AKI can progress into chronic kidney injury [3]. Several perioperative factors, such as a high model for end-stage liver disease (MELD) scores, pre-LT renal dysfunction, graft quality, and intraoperative hemodynamic instability, are reported to be associated with post-LT AKI [2, 4, 5]. In recent times, inflammation has been considered to be the potential mechanism in the development of AKI [6, 7].

Antithrombin III (ATIII), produced by the liver, has both anti-coagulative and anti- inflammatory effects [8]. Previous studies regarding LT surgery focused only on the effect of ATIII as a serine protease inhibitor in the coagulation cascade to prevent hepatic artery thrombosis or portal vein thrombosis [9, 10]. The reno-protective potential of ATIII has been consistently supported by evidences from numerous animal studies [11, 12].

Patients with end-stage liver disease (ESLD) are known to have a low level of ATIII, which might due to impaired hepatic synthesis and increase consumption of ATIII [13]. In addition, systemic inflammatory reaction and the associated immunological imbalance are believed to form the combined pathophysiological pathway of ESLD [6]. Moreover, the role of inflammation has been receiving increasing focus as a key factor for postoperative AKI [7, 14, 15].

We hypothesized that the anti-inflammatory effect of ATIII might have a role in preventing post-LT AKI. This study aimed to determine the relationship between ATIII level and post-LT AKI. In addition, we evaluated the incidence of early allograft dysfunction (EAD), graft failure, chronic kidney disease (CKD), and overall mortality.

Methods

Study population

This retrospective observational study was approved by the institutional review board (IRB) of our center (No.2019 − 1699) and the requirement for written informed consent was waived by the IRB.
The data of all patients who underwent either living- or deceased-donor LT (LDLT, DDLT) from April 2010 to January 2018 were reviewed. Of the 3034 adults (≥ 18 years of age) identified, those who underwent re-transplantation (n = 85), who were previously diagnosed with end-stage renal disease or CKD (n = 24), who were being treated with continuous renal replacement therapy (n = 411), and whose preoperative (n = 72) or postoperative (n = 47) ATIII levels were not available were excluded. Finally, 2395 patients were included in our final analysis (Fig. 1).

Perioperative ATIII administration and measurement

ATIII levels were measured preoperatively and postoperatively in all LT recipients according to our institution's routine protocol. Preoperative ATIII values were measured on the day before transplant in all LT recipients. The study population was divided into two groups based on their preoperative ATIII values: preoperative ATIII ≥ 50% (ATIII ≥ 50% group) vs. preoperative ATIII < 50% (ATIII < 50% group). For all recipients, regardless of the preoperative ATIII level, 2000 units of exogenous ATIII was administered daily for seven consecutive days beginning on the day after transplantation, according to our institution's protocol. In addition, in recipients with baseline ATIII level lower than 50% (ATIII < 50% group), exogenous ATIII (SK Anti-Thrombin III; SK plasma, Osan, South Korea) was administered during the anhepatic phase of the LT surgery, according to our institution's protocol. The dose to be administered was calculated as follows:

$$Exogenous\ dose\ of\ ATIII\ (units) = [100 - baseline\ ATIII\ value\ (\%)] \times body\ weight\ (kg) \times 0.8$$

Data acquisition

All clinical data were gained from computerized medical record system. Baseline characteristics included age, sex, body mass index (BMI), presence of underlying disease (diabetes mellitus, hypertension, coronary artery disease), MELD score, cause for liver transplant (hepatitis virus, alcoholic cirrhosis, malignancy, or others), and comorbidities due to ESLD (varix bleeding, hepatic encephalopathy, or pleural effusion). Preoperative laboratory variables included the level of ATIII, platelet count, total bilirubin, albumin, prothrombin time-international normalized ratio (INR), creatinine, and C-reactive protein. Perioperative variables comprised donor type (deceased vs. living), duration of surgery, graft-to-recipient weight ratio (GRWR), total ischemic time, amount of blood transfusion, and tacrolimus trough level on postoperative day (POD) 7.

Postoperative outcomes

The primary outcome was the occurrence of postoperative AKI, which was defined as serum creatinine ≥ 0.3 mg/dL within POD 2 or increase by ≥ 1.5 times within POD 7 according to the criteria set by the Kidney Disease: Improving Global Outcomes (KDIGO) classification [16]. It is further divided into three grades of AKI as follows: grade 1, an increase in creatinine ≥ 0.3 mg/dL within POD 2 or 1.5–1.9 times from the baseline within POD 7; grade 2, an increase in creatinine 2.0–2.9 times from the baseline within POD 7; grade 3, an increase in creatinine more than 3 times from baseline within POD 7, creatinine value ≥ 4.0 mg/dL with an increase of at least 0.5 mg/dL within POD 7, or patients requiring renal replacement therapy within POD 7.

The secondary outcomes included progression to CKD, EAD, graft failure, and overall mortality. The occurrence of CKD was defined as the glomerular filtration rate less than 60 $mL \bullet min^{-1} \bullet 1.73m^{-2}$ on two consecutive occasions at least 3 months apart [17]. EAD was defined as the presence of at least one of the following: total bilirubin ≥ 10 mg/dL on POD7, prothrombin time (INR) ≥ 1.6 on POD 7, and alanine or aspartate aminotransferases > 2000 IU/L within POD 7 [18].

Statistical analysis

Values are expressed as numbers (percentages), mean ± standard deviation, or as median [interquartile range (IQR)] according to the normality of the data. Analyses between the groups were performed using the student's *t*-test, Mann–Whiney U test, analysis of variance, logistic regression, or Kruskal–Wallis test for continuous variables and χ^2 test or Fisher's exact test for categorical variables, as appropriate. Significant variables with a *P* value < 0.1 in the univariate analysis were entered into the multivariate logistic regression model using backward elimination. Subgroup analyses according to the MELD scores (< 20, ≥ 20) and donor types (deceased vs. living) were performed to investigate the prognostic value of ATIII levels. All *P* values < 0.05 were considered statistically significant. All statistical analysis and graphical representations were performed using the R software version 3.3.2 (http://www.r-project.org) and Prism software version 7 (GraphPad, San Diego, CA, USA).

Results

Baseline characteristics

Table 1 demonstrates the baseline characteristics of the patients according to the groups based on ATIII levels (< 50%, ≥ 50%). The total cohort of 2,395 patients had a mean age of 53.1 ± 8.5 years and a median (IQR) MELD score of 13 (9–18), while male patients comprised 74.7% of the study population. Causes for liver transplant were hepatitis virus-related liver cirrhosis (67.4%), alcoholic liver cirrhosis (18.6%), and others (14.1%). The majority of the study population underwent living-donor LT (93.2%). The mean duration of surgery was 13.1 hours, and 26.7% of the patients received a massive transfusion of 10 units of packed red blood cells (pRBC) or more during the operation.

Table 1
Patients' demographics according to the preoperative Antithrombin III level

	Antithrombin III < 50% (N = 1451,60.6%)	Antithrombin III ≥ 50 % (N = 944, 39.4%)	Total (N = 2395)	*P* value
Demographic data				
Age (years)	52.8 ± 8.6	53.5 ± 8.2	53.1 ± 8.5	0.036
Sex (male sex)	1059 (73.0%)	730 (77.3%)	1789 (74.7%)	0.019
Body mass index (m/kg^2)	24.0 ± 3.7	23.8 ± 3.2	23.9 ± 3.5	0.304
Diabetes	350 (24.1%)	207 (21.9%)	557 (23.3%)	0.233
Hypertension	191 (13.2%)	203 (21.5%)	394 (16.5%)	< 0.001
Coronary artery disease	13 (0.9%)	13 (1.4%)	26 (1.1%)	0.363
MELD score	16 (12–23)	8.5 (7–11)	13 (9–18)	< 0.001
MELD score over 20	462 (31.8%)	19 (2.0%)	481 (20.1%)	< 0.001
Causes for liver transplant				< 0.001
HBV-related liver cirrhosis	526 (67.1%)	922 (57.2%)	1448 (60.5%)	
HCV-related liver cirrhosis	42 (5.4%)	123 (7.6%)	165 (6.9%)	
Alcoholic liver cirrhosis	118 (15.1%)	327 (20.3%)	445 (18.6%)	
Others	98 (12.5%)	239 (14.8%)	337 (14.1%)	
Hepatocellular carcinoma	452 (57.7%)	782 (48.5%)	1234 (51.5%)	
Comorbidities				
Varix bleeding	386 (26.6%)	248 (26.3%)	634 (26.5%)	0.895
Hepatic encephalopathy	273 (18.8%)	22 (2.3%)	295 (12.3%)	< 0.001
Pleural effusion	252 (17.4%)	51 (5.4%)	303 (12.7%)	< 0.001

	Antithrombin III < 50% (N = 1451,60.6%)	Antithrombin III ≥ 50 % (N = 944, 39.4%)	Total (N = 2395)	*P* value
Preoperative laboratory variables				
Antithrombin III (%)	30.2 ± 11.8	67.1 ± 13.2	44.8 ± 21.9	< 0.001
Platelet count (×10^3/μL)	65.3 ± 43.1	90.3 ± 58.4	75.1 ± 51.2	< 0.001
Total bilirubin (mg/dL)	8.3 ± 10.5	1.8 ± 4.0	5.7 ± 9.1	< 0.001
Albumin (g/dL)	3.0 ± 0.6	3.4 ± 0.5	3.1 ± 0.6	< 0.001
Prothrombin time (INR)	1.9 ± 1.2	1.2 ± 0.2	1.6 ± 1.0	< 0.001
Creatinine (mg/dL)	0.8 ± 0.5	0.8 ± 0.3	0.8 ± 0.4	0.502
C-reactive protein (mg/L)	0.8 ± 1.1	0.4 ± 0.9	0.7 ± 1.1	< 0.001
Operative variables				
Deceased-donor	149 (10.3%)	15 (1.6%)	164 (6.8%)	< 0.001
Living-donor	762 (97.2%)	1469 (91.2%)	2231 (93.2%)	0.001
Duration of surgery (min)	800.2 ± 151.0	758.0 ± 135.2	783.6 ± 146.4	< 0.001
Graft-to-recipient weight ratio (g/kg)	1.2 ± 0.5	1.1 ± 0.3	1.2 ± 0.4	< 0.001
Total ischemic time (min)	147.5 ± 71.7	130.5 ± 53.4	140.8 ± 65.6	< 0.001
Transfusion				
pRBC (unit)	10.4 ± 14.7	3.4 ± 6.8	7.7 ± 12.7	< 0.001
Massive transfusion	535 (36.9%)	104 (11.0%)	639 (26.7%)	< 0.001
FFP (unit)	10.8 ± 14.9	3.5 ± 7.0	7.9 ± 12.9	< 0.001
Cryoprecipitate (unit)	8.1 ± 8.9	2.8 ± 5.2	6.0 ± 8.1	< 0.001

	Antithrombin III < 50% (N = 1451,60.6%)	Antithrombin III ≥ 50 % (N = 944, 39.4%)	Total (N = 2395)	*P* value
Platelet apheresis (unit)	0.8 ± 1.0	0.3 ± 0.6	0.6 ± 0.9	< 0.001
Tacrolimus trough level within POD 7	5.2 ± 2.6	6.0 ± 2.5	5.5 ± 2.6	< 0.001

Continuous variables are expressed as mean ± standard deviation or as median (interquartile range) and categorical variables as n (%).

*Massive transfusion: transfusion of > 10 units of packed red blood cells

MELD score, Model for End-stage Liver Disease score; IQR, interquartile range; INR, International Normalized Ratio; pRBC, packed red blood cells; FFP, Fresh frozen plasma; POD, postoperative day.

Perioperative AT III value

In all, 15,884 perioperative ATIII values were measured from the day before transplant to POD 7. Preoperative ATIII values were measured for all 2,395 patients. Postoperative ATIII was measured at least once for each patient within POD 7. By POD 2, 97.1% of the total patients had at least one postoperative ATIII value measured. The mean preoperative ATIII value was 44.8 ± 21.9% (67.1 ± 13.2% in the ATIII ≥ 50% group vs. 30.2 ± 11.8% in the ATIII < 50% group, $P < 0.001$). Of the 1,451 (60.6%) patients, who had preoperative ATIII value lower than 50% (ATIII < 50% group), received additional intraoperative exogenous ATIII in a dose calculated by our institution's protocol. Postoperative ATIII level showed an increasing trend in both groups. ATIII levels in ATIII ≥ 50% group were higher than those in the AT < 50% group, except on POD 1 where the ATIII value of ATIII < 50% group transiently exceeded that of ATIII ≥ 50% group due to the additional intraoperative administration of recombinant ATIII (64.0 ± 18.2% for ATIII ≥ 50% group vs. 79.0 ± 21.6% for ATIII < 50% group, $P < 0.001$, Supplementary Fig. 1).

Incidence of postoperative acute kidney injury and its relationship with ATIII value

Postoperative AKI occurred in 67.3% of the total population. Grade 2 and 3 comprised 3.5% and 3.6% of total incidents of postoperative AKI, respectively (Table 2). Based on the preoperative ATIII value, the rate of postoperative AKI was significantly higher in the ATIII < 50% group than in the ATIII ≥ 50% group (75.5% vs. 54.7%, $P < 0.001$, Table 2). The probability of postoperative AKI decreased with the increasing value of preoperative ATIII (Fig. 2A).

Table 2
Postoperative outcomes according to preoperative Antithrombin III levels

	Preoperative Antithrombin III < 50% (N = 1451)	Preoperative Antithrombin III ≥ 50% (N = 944)	Total (N = 2395)	*P* value
Postoperative renal outcomes				
Acute kidney injury	1095 (75.5%)	516 (54.7%)	1611 (67.3%)	< 0.001
Grades of acute kidney injury				< 0.001
1	970 (66.9%)	472 (50.0%)	1442 (60.2%)	< 0.001
2	49 (3.4%)	34 (3.6%)	83 (3.5%)	0.858
3	76 (5.2%)	10 (1.1%)	86 (3.6%)	< 0.001
Chronic kidney disease				
At 3 months after liver transplant	474 (34.1%)	272 (29.6%)	746 (32.3%)	0.029
At 6 months after liver transplant	551 (39.6%)	306 (33.3%)	857 (37.1%)	0.003
At 1 year after liver transplant	490 (37.6%)	283 (33.1%)	773 (35.8%)	0.036
Other postoperative outcomes				
Early allograft dysfunction	222 (15.3%)	38 (4.0%)	260 (10.9%)	< 0.001
Overall graft failure	115 (7.9%)	67 (7.1%)	182 (7.6%)	0.504
Overall mortality	109 (7.5%)	63 (6.7%)	172 (7.2%)	0.487

In the multivariate analysis, preoperative ATIII remained as an independent predictor for postoperative AKI (adjusted odds ratio [OR, per 10% increase], 0.86; 95% confidence interval [CI] 0.81–0.92; $P < 0.001$) along with female sex (OR 1.26; 95% CI 1.01–1.57; $P = 0.035$), body mass index (OR 1.09; 95% CI 1.06–1.12; $P < 0.001$), serum albumin level (OR 0.62; 95% CI 0.53–0.74; $P < 0.001$), deceased-donor LT (OR 6.69; 95% CI 3.22–13.93; $P < 0.001$), duration of surgery (OR [per an hour increase] 1.14; 95% CI 1.09–1.20; $P < 0.001$), and pRBC transfusion (OR [per 5 units increase] 1.08; 95% CI 1.02–1.14; $P = 0.009$) (Table 3). Figure 2B shows the plotted multivariate-adjusted relative risk of postoperative AKI in relation with preoperative ATIII level.

Table 3
Multivariate analysis of risk factors associated with postoperative acute kidney injury

	All patients (N = 2395)			
	Crude OR (95% CI)	P **value**	**Multivariate OR (95% CI)**	P **value**
Preoperative antithrombin III (per 10% increase)	0.81 (0.78–0.84)	< 0.001	0.86 (0.81–0.92)	< 0.001
Age	1.00 (1.00–1.01)	0.257		
Female sex	1.23 (1.01–1.51)	0.041	1.26 (1.01–1.57)	0.035
Body mass index	1.09 (1.07–1.12)	< 0.001	1.09 (1.06–1.12)	< 0.001
Diabetes mellitus	1.30 (1.06–1.61)	0.012		
Hypertension	1.22 (0.96–1.54)	0.101		
Hepatic encephalopathy	1.66 (1.25–2.20)	< 0.001		
MELD score	1.04 (1.03–1.06)	< 0.001		
Albumin	0.50 (0.43–0.58)	< 0.001	0.62 (0.53–0.74)	< 0.001
C-reactive protein	1.15 (1.05–1.26)	0.003		
Deceased-donor LT	3.35 (2.12–5.29)	< 0.001	6.69 (3.22–13.93)	< 0.001
Operation time (per an hour increase)	1.14 (1.10–1.19)	< 0.001	1.14 (1.09– 1.20)	< 0.001
pRBC transfusion (per 5 units)	1.20 (1.14–1.27)	< 0.001	1.08 (1.02–1.14)	0.009
Graft-to-recipient weight ratio	1.21 (0.98–1.49)	0.082		
Total ischemic time (per 10 minute)	1.04 (1.02–1.05)	< 0.001		

OR, odds ratio; CI, confidence interval; LT: liver transplantation; MELD score, Model for End-stage Liver Disease score; pRBC, packed red blood cells

Development of chronic kidney disease after postoperative acute kidney injury

CKD developed in 32.3%, 37.1%, and 35.8% of the patients after 3 months, 6 months, and 1 year of LT, respectively. Patients with ATIII < 50% are prone to postoperative CKD ($P = 0.036$, Table 2). AKI can lead to a higher prevalence of CKD at 3 months, 6 months, and 1 year after LT (all $P < 0.001$, Fig. 3). Moreover, patients with ATIII < 50% showed a higher incidence of EAD (15.3% vs. 4.0%, $P < 0.001$). However, the

overall graft failure and overall mortality after LT were not different according to the preoperative ATIII level (Table 2).

Subgroup analysis according to the MELD scores and donor types

The patients were further divided into subgroups based on MELD scores (≥ 20, < 20) and donor types (deceased vs. living) to evaluate the predictive value of the ATIII. In the subgroups divided by MELD score, ATIII had a preventive effect on AKI in patients with MELD scores < 20 (OR 0.82, 95% CI 0.77–0.87, *P* < 0.001, supplement Fig. 2). In contrast, ATIII did not have a statistically significant preventive effect in patients with MELD score ≥ 20. In patients who underwent DDLT, the median MELD score was 26, while it was 12 in patients who underwent LDLT. ATIII level was 22% in the DDLT subgroup and 45% in the LDLT subgroup. AKI incidence was higher in DDLT (86.6% vs. 65.8%, *P* < 0.001). When analyzing the ATIII value by donor types (deceased vs. living), the predictive value of ATIII for AKI in LDLT was statistically significant (OR 0.89, CI 0.85–0.94, *P* < 0.001).

Discussion

In this retrospective observational study, we found that the preoperative level of ATIII was associated with postoperative AKI in over 2,300 patients undergoing LT. In multivariate analysis, a 10% increase in preoperative ATIII was associated with 0.86 times decreased risk of post-LT AKI. This association between the preoperative ATIII level and post-LT AKI remained significant only in the low-MELD (< 20) and LDLT subgroups. Additionally, low ATIII was associated with progression to CKD and EAD.

Most previous studies that explored the relationship between ATIII and AKI were performed in animal models; hence, the data in humans are limited [11, 12, 19, 20]. A previous study by Wang et al. demonstrated the predictive value of ATIII level in the development of AKI [11]. The authors concluded that ATIII appears to ameliorate renal ischemia-reperfusion injury by inhibiting the inflammatory response, oxidative stress, apoptosis, and by improving the renal blood flow. The authors also presented human clinical data, which included only 7 patients with low ATIII levels (< 75%), while the majority of patients had normal ATIII levels. Another recent study by Park et al. demonstrated the relationship between preoperative low ATIII level (< 70%) and AKI following LDLT [21]. The authors suggested that the incidence of AKI was 24.8% (143/577) following LDLT, which was much lower than that in our study (67.3%, 1611/2395). This difference in the incidence of AKI might be due to the difference in the study population. In our study, we included DDLT recipients who were at high risk for the development of post-LT AKI. As the patients' severity increased, the duration of surgery was about 4 hours longer than that in the previous study [21]. A previous study showed that duration of surgery > 10 hours was an independent risk factor for post-LT AKI, which is in line with the finding of our study [22]. In addition, our results showed that the rate of a high amount of transfusion (> 10 units of pRBC) was 26.7%, which is one of the risk factors of AKI.

Our center's protocol of ATIII administration during the perioperative period resulted in a rapid increase of ATIII level. We uniformly administered 2000 units of ATIII daily from POD1 to POD7. Kaneko et al.

reported that the ATIII level did not return to normal after LDLT during the first 2 weeks [23]. In a previous study, an initial ATIII level < 50% was reported as the best prognosticator for the prediction of mortality from septic shock [24]. Hence, only patients with preoperative ATIII level < 50% were administered an additional dose of ATIII during the surgery. As a consequence, the average level of ATIII reached the normal level from POD 2 (88.6 ± 18.4% for ATIII ≥ 50% group and 85.9 ± 17.5% for AT III < 50% group). However, on POD7, the ATIII level exceeded the normal (135.1 ± 24.1% in the ATIII ≥ 50% group and 124.2 ± 21.3% for ATIII < 50% group). A protocol with individualized dosage based on the ATIII level might be more cost-effective for maintaining a consistent level of ATIII during the post-LT period.

In our study, low ATIII level, female sex, high BMI, low serum albumin, DDLT, longer duration of surgery, and higher amount of pRBC transfusion were considered as risk factors for the development of post-LT AKI. Similarly, a previous study also reported that female sex, obesity, low serum albumin, DDLT, longer duration of surgery, and higher amount of blood transfusions were associated the development of post-LT AKI [1, 2, 22, 25]. In our study, the MELD score was not a risk factor for post-LT AKI. Since we excluded patients who were previously diagnosed with end-stage renal disease or CKD, the MELD score did not significantly impact the incidence of post-LT AKI. According to our results, preoperative ATIII level as a prognostic factor for predicting AKI remained significant only in the low-MELD group (< 20) and LDLT subgroups but was not statistically significant in the high-MELD group(≥ 20) and DDLT subgroups. Given that the incidence of AKI in the DDLT group was more than 80% in our study, the DDLT group might have multiple factors that might have led to post-LT AKI. Consistent with our findings, other studies also reported that the DDLT group had a higher incidence of post-LT AKI than the LDLT group [25].

In our study, more than 50% of the patients developed post-LT AKI, and a significant proportion of them progressed to CKD after LT surgery. Although most of them were grade I AKI (89.5%, 1442/1611), over one-third of them progressed to CKD (32.3% at 3 months, 37.1% at 6 months, 35.8% at 1 year after LT). Given that the development of AKI and CKD in LT recipients are considered as the important risk factors for post-LT morbidity and mortality [26], strategies to prevent AKI should be implemented in the peri-LT period. In addition, considering the relatively high rate of postoperative AKI in LT surgery compared to that in other non-cardiac surgeries, there is more room for improvement [27].

There are several limitations to this study. First, we could not explain the mechanism of the preventive role of ATIII on the development of post-LT AKI. However, a previous study reported that ATIII insufficiency exacerbates the renal ischemia-reperfusion injury by inflammation, oxidative stress, and apoptosis [11], which are well-known mechanisms associated with the development of AKI. Second, since this was a retrospective study, the confounding factors could not be eliminated entirely. Third, there is no clear evidence regarding the optimal perioperative dose of ATIII to prevent AKI in LT recipients. Although the ATIII level could be normalized during the first two weeks after LT [23], it is necessary to know the target level of ATIII to mitigate the incidence of post-LT AKI. Therefore, further studies are necessary for the individualization of the ATIII dose based on the preoperative ATIII level.

Conclusions

In conclusion, we found that a low level of ATIII is significantly associated with post-LT AKI. Notably, the preoperative ATIII might have a prognostic value for post-LT AKI in patients with low MELD score (< 20) and those undergoing LDLT.

Abbreviations

ATIII
Antithrombin III
LT
liver transplantation
AKI
Acute kidney injury
Post-LT AKI
Acute kidney injury after liver transplantation
ESLD
end-stage liver disease
EAD
early allograft dysfunction
CKD
chronic kidney disease
LDLT
living-donor liver transplantation
DDLT
deceased-donor liver transplantation
BMI
body mass index
MELD
Model for End-stage liver disease
INR
international normalized ratio
GRWR
graft-to-recipient weight ratio
POD
postoperative day
KDIGO
Kidney Disease:Improving Global Outcomes
IQR
interquartile range
pRBC
packed red blood cells

OR
odds ratio
CI
confidence interval

Declarations

Ethics approval and consent to participate: This retrospective observational study was approved by the institutional review board of our center (No.2019-1699).

Consent for publication: Not applicable

Availability of data and materials: The datasets used for the analysis in the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

Funding: None.

Authors' contributions:

Y.-J.M., and J.-G.S. conceived and designed study. K.-S.K.,S.-H.K. and H.-M.K. were involved in data acquisition; Y.-J.M.,I.-G.J.,and G.-S.H. were involved in analysis and/or interpretation of data; K.-S.K.,Y.-J.M., and J.-G.S drafted the manuscript; J.-G.S. revised the manuscript critically for important intellectual content. All authors gave approval for the final manuscript.

Acknowledgements: None.

References

1. Chen J, Singhapricha T, Hu KQ, Hong JC, Steadman RH, Busuttil RW, Xia VW: **Postliver transplant acute renal injury and failure by the RIFLE criteria in patients with normal pretransplant serum creatinine concentrations: a matched study**. *Transplantation* 2011, **91**(3):348-353.
2. Hilmi IA, Damian D, Al-Khafaji A, Planinsic R, Boucek C, Sakai T, Chang CC, Kellum JA: **Acute kidney injury following orthotopic liver transplantation: incidence, risk factors, and effects on patient and graft outcomes**. *Br J Anaesth* 2015, **114**(6):919-926.
3. Chawla LS, Kimmel PL: **Acute kidney injury and chronic kidney disease: an integrated clinical syndrome**. *Kidney Int* 2012, **82**(5):516-524.
4. Inoue Y, Soyama A, Takatsuki M, Hidaka M, Muraoka I, Kanematsu T, Eguchi S: **Acute kidney injury following living donor liver transplantation**. *Clin Transplant* 2012, **26**(5):E530-535.
5. Rahman S, Davidson BR, Mallett SV: **Early acute kidney injury after liver transplantation: Predisposing factors and clinical implications**. *World J Hepatol* 2017, **9**(18):823-832.

6. Claria J, Stauber RE, Coenraad MJ, Moreau R, Jalan R, Pavesi M, Amoros A, Titos E, Alcaraz-Quiles J, Oettl K *et al*: **Systemic inflammation in decompensated cirrhosis: Characterization and role in acute-on-chronic liver failure**. *Hepatology* 2016, **64**(4):1249-1264.
7. Chae MS, Kim Y, Chung HS, Park CS, Lee J, Choi JH, Hong SH: **Predictive Role of Serum Cytokine Profiles in Acute Kidney Injury after Living Donor Liver Transplantation**. *Mediators Inflamm* 2018, **2018**:8256193.
8. Levy JH, Sniecinski RM, Welsby IJ, Levi M: **Antithrombin: anti-inflammatory properties and clinical applications**. *Thromb Haemost* 2016, **115**(4):712-728.
9. Hashikura Y, Kawasaki S, Okumura N, Ishikawa S, Matsunami H, Ikegami T, Nakazawa Y, Makuuchi M: **Prevention of hepatic artery thrombosis in pediatric liver transplantation**. *Transplantation* 1995, **60**(10):1109-1112.
10. Kawanaka H, Akahoshi T, Kinjo N, Konishi K, Yoshida D, Anegawa G, Yamaguchi S, Uehara H, Hashimoto N, Tsutsumi N *et al*: **Impact of antithrombin III concentrates on portal vein thrombosis after splenectomy in patients with liver cirrhosis and hypersplenism**. *Ann Surg* 2010, **251**(1):76-83.
11. Wang F, Zhang G, Lu Z, Geurts AM, Usa K, Jacob HJ, Cowley AW, Wang N, Liang M: **Antithrombin III/SerpinC1 insufficiency exacerbates renal ischemia/reperfusion injury**. *Kidney Int* 2015, **88**(4):796-803.
12. Yin J, Wang F, Kong Y, Wu R, Zhang G, Wang N, Wang L, Lu Z, Liang M: **Antithrombin III prevents progression of chronic kidney disease following experimental ischaemic-reperfusion injury**. *J Cell Mol Med* 2017, **21**(12):3506-3514.
13. Knot E, Ten Cate JW, Drijfhout HR, Kahlé LH, Tytgat GN: **Antithrombin III metabolism in patients with liver disease**. *J Clin Pathol* 1984, **37**(5):523-530.
14. Goren O, Matot I: **Perioperative acute kidney injury**. *Br J Anaesth* 2015, **115 Suppl 2**:ii3-14.
15. Rabb H, Griffin MD, McKay DB, Swaminathan S, Pickkers P, Rosner MH, Kellum JA, Ronco C, Acute Dialysis Quality Initiative Consensus XWG: **Inflammation in AKI: Current Understanding, Key Questions, and Knowledge Gaps**. *J Am Soc Nephrol* 2016, **27**(2):371-379.
16. Inker LA, Astor BC, Fox CH, Isakova T, Lash JP, Peralta CA, Kurella Tamura M, Feldman HI: **KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD**. *Am J Kidney Dis* 2014, **63**(5):713-735.
17. Levey AS, de Jong PE, Coresh J, El Nahas M, Astor BC, Matsushita K, Gansevoort RT, Kasiske BL, Eckardt KU: **The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report**. *Kidney Int* 2011, **80**(1):17-28.
18. Olthoff KM, Kulik L, Samstein B, Kaminski M, Abecassis M, Emond J, Shaked A, Christie JD: **Validation of a current definition of early allograft dysfunction in liver transplant recipients and analysis of risk factors**. *Liver Transpl* 2010, **16**(8):943-949.
19. Wu R, Kong Y, Yin J, Liang R, Lu Z, Wang N, Zhao Q, Zhou Y, Yan C, Wang F *et al*: **Antithrombin is a Novel Predictor for Contrast Induced Nephropathy After Coronary Angiography**. *Kidney Blood Press Res* 2018, **43**(1):170-180.

20. Lu Z, Cheng D, Yin J, Wu R, Zhang G, Zhao Q, Wang N, Wang F, Liang M: **Antithrombin III Protects Against Contrast-Induced Nephropathy**. *EBioMedicine* 2017, **17**:101-107.
21. Park J, Cho S, Cho YJ, Choi HJ, Hong SH, Chae MS: **Predictive Utility of Antithrombin III in Acute Kidney Injury in Living-Donor Liver Transplantation: A Retrospective Observational Cohort Study**. *Transplant Proc* 2020.
22. Park MH, Shim HS, Kim WH, Kim HJ, Kim DJ, Lee SH, Kim CS, Gwak MS, Kim GS: **Clinical Risk Scoring Models for Prediction of Acute Kidney Injury after Living Donor Liver Transplantation: A Retrospective Observational Study**. *PLoS One* 2015, **10**(8):e0136230.
23. Kaneko J, Sugawara Y, Tamura S, Togashi J, Matsui Y, Makuuchi M: **Antithrombin effect on coagulation and fibrinolytic profiles after living donor liver transplantation: a pilot study**. *Int J Lab Hematol* 2009, **31**(1):81-86.
24. Fourrier F, Chopin C, Goudemand J, Hendrycx S, Caron C, Rime A, Marey A, Lestavel P: **Septic shock, multiple organ failure, and disseminated intravascular coagulation. Compared patterns of antithrombin III, protein C, and protein S deficiencies**. *Chest* 1992, **101**(3):816-823.
25. Hilmi IA, Damian D, Al-Khafaji A, Sakai T, Donaldson J, Winger DG, Kellum JA: **Acute kidney injury after orthotopic liver transplantation using living donor versus deceased donor grafts: A propensity score-matched analysis**. *Liver Transpl* 2015, **21**(9):1179-1185.
26. Weber ML, Ibrahim HN, Lake JR: **Renal dysfunction in liver transplant recipients: evaluation of the critical issues**. *Liver Transpl* 2012, **18**(11):1290-1301.
27. Abelha FJ, Botelho M, Fernandes V, Barros H: **Determinants of postoperative acute kidney injury**. *Crit Care* 2009, **13**(3):R79.

Figures

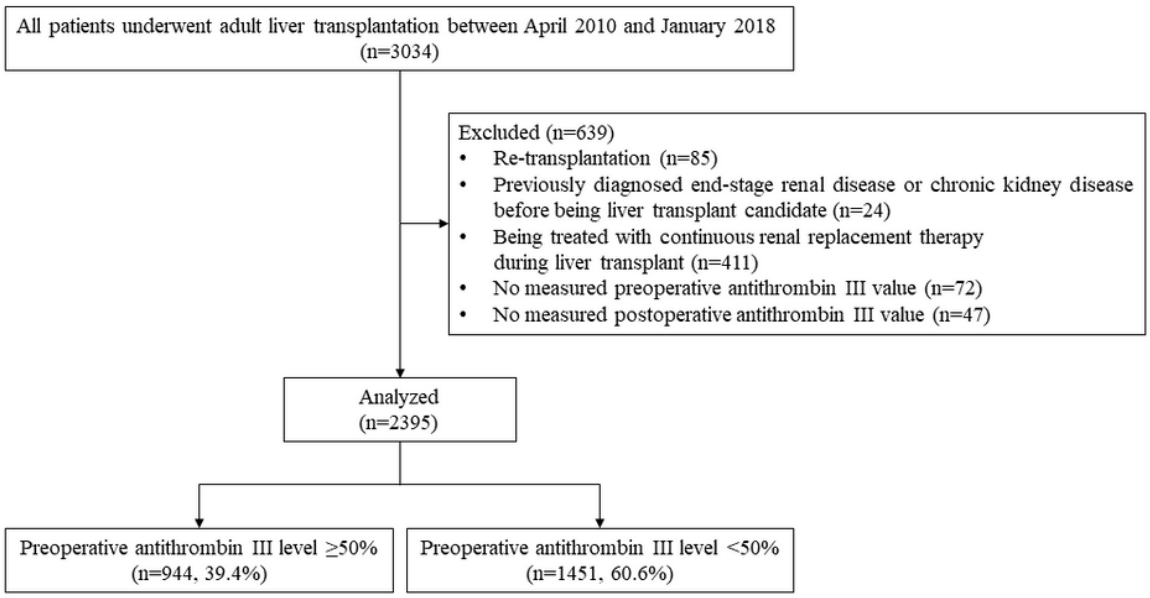

Figure 1

Flow diagram of the patient inclusion and exclusion.

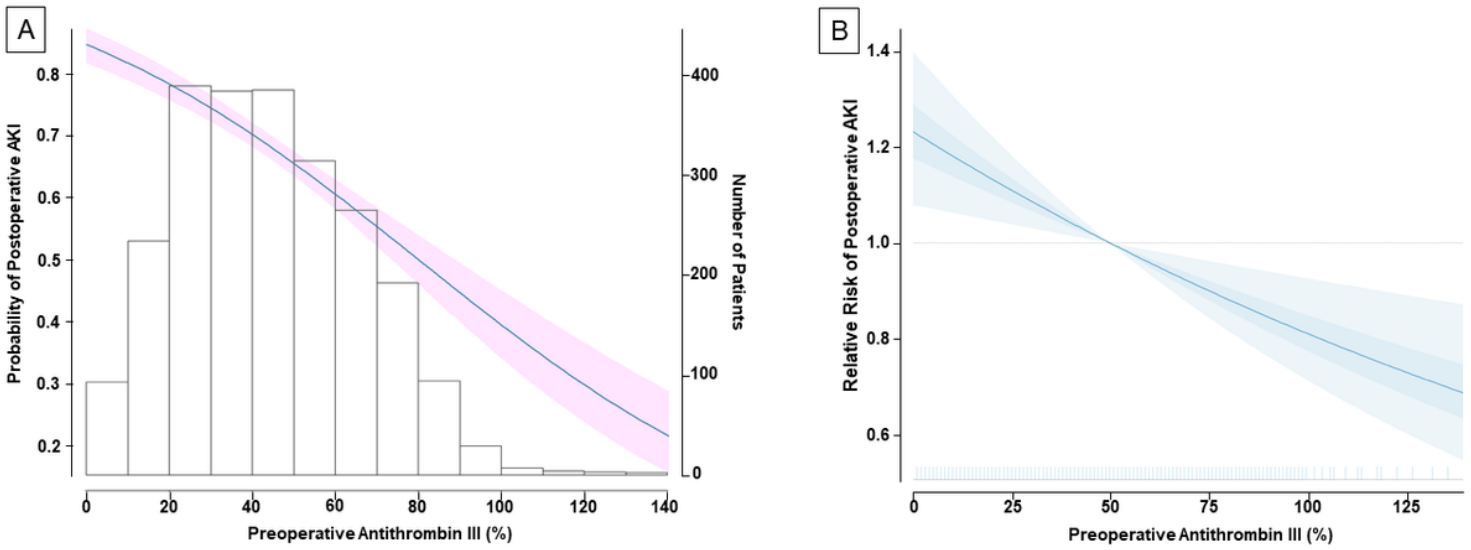

Figure 2

The association between preoperative antithrombin III and postoperative acute kidney injury. The solid line indicates the probability on a continuous scale value, and the shaded areas indicate 95% confidence interval (A). The multivariate-adjusted relative risk plot showing the relationship between preoperative ATIII and postoperative acute kidney injury (B). Estimates are adjusted for independent confounders from multivariable generalized logistic regression model. The solid lines and translucent band depict relative risk and 95% confidence intervals of those estimates.

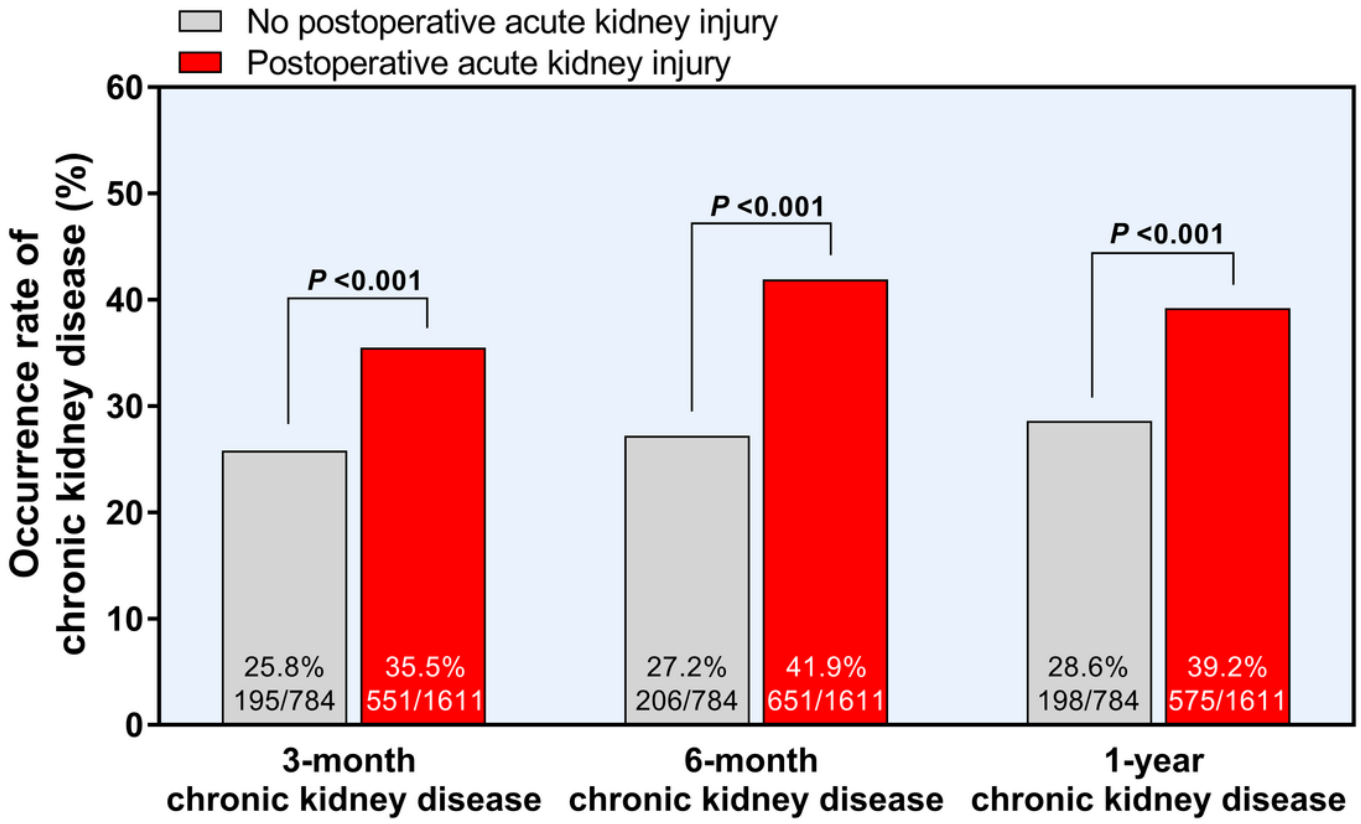

Figure 3

Development of chronic kidney disease after postoperative acute kidney injury

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- ATIIIsuppFig1.png
- ATIIIsuppFig2.tiff