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Title: Association of antenatal antithrombin activity with perinatal liver dysfunction: prospective multicenter study

Running title: Antithrombin deficiency in pregnancy

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Abstract

Background and Aim: Liver dysfunction with decreased antithrombin activity (AT) and/or thrombocytopenia is life-threatening in pregnant women. Whether AT is clinically useful for prediction of liver dysfunction remains unclear.

Methods: A total of 541 women were registered prospectively at gestational week 34.7 (20.0 – 41.4) with available data on antenatal AT and platelet count (PLC).

Results: Liver dysfunction defined as serum AST > 45 IU/L concomitant with lactate dehydrogenase (LDH) > 400 IU/L occurred in five women antenatally (≤ 2 weeks before delivery) and in 17 women postpartum (within 1 week postpartum). Median (5^{th} – 95^{th}) antenatal value was 85 (62 – 110)% for AT and 202 (118 – 315)×10^9/L for PLC in the 541 women, and was significantly lower in women with than without perinatal liver dysfunction; 75 (51 – 108) vs. 86 (62 – 110)% and 179 (56 – 244) vs. 203 (121 – 316)×10^9/L, respectively. Nineteen (86%) women with liver dysfunction showed AT ≤ 62% or thrombocytopenia (PLC ≤ 118×10^9/L) perinatally, but five lacked thrombocytopenia throughout the perinatal period. The best cut-off (AT, 77%; PLC, 139×10^9/L) suggested by receiver operating characteristic curve gave antenatal AT and PLC sensitivity of 59% and 41% with positive predictive value (PPV) of 8.6% and 14%, respectively, and combined use of AT and PLC improved sensitivity to 73% (16/22) with PPV of 9.2% for prediction of perinatal liver dysfunction.

Conclusions: Reduced AT not accompanied by thrombocytopenia can precede liver dysfunction. Clinical introduction of AT may enhance safety of pregnant women.

Key words: acute fatty liver of pregnancy; antithrombin activity; disseminated intravascular coagulation; HELLP syndrome; maternal mortality; pregnancy complication

Abbreviations:
AFLP, acute fatty liver of pregnancy
AST, aspartate aminotransferase
AT, antithrombin
AUC, area under the curve
DIC, disseminated intravascular coagulation
GW, gestational week
HDP, hypertensive disorders of pregnancy
HELLP syndrome, syndrome of hemolysis, elevated liver enzymes, and low platelets
LDH, lactate dehydrogenase
NPV, negative predictive value
PIATD, pregnancy-induced antithrombin deficiency
PLC, platelet counts
PPD, postpartum day
PPV, positive predictive value

ROC, receiver operating characteristic curve

Introduction

Liver dysfunction evidenced by elevated serum aspartate aminotransaminase (AST) level occurs in 3.2% of pregnant women peripartum.[1] Liver dysfunction associated with the syndrome of hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome), acute fatty liver of pregnancy (AFLP), and hypertensive disorders of pregnancy (HDP) are life-threatening conditions,[1 - 6] and elevated lactate dehydrogenase (LDH) level is seen concomitantly in such women.[7,8] Women with HDP and or gestational thrombocytopenia are likely to develop liver dysfunction.[1 - 3, 9 - 11] Recent guidelines recommend the use of blood tests including platelet counts to monitor multiorgan involvement in patients with HDP.[12 - 16]

However, liver dysfunction can occur even in the absence of HDP or thrombocytopenia; some patients with AFLP lack thrombocytopenia and hypertension, but have liver dysfunction at presentation.[2,3,5,17,18] As consumption coagulopathy leading to disseminated intravascular coagulation (DIC) may be a major problem and as baseline abnormalities on laboratory data at presentation may be associated with outcome in women with HELLP syndrome and AFLP, early suspicion may be important to improve outcome of these patients.[19,20] In a series of case reports and reports on case series regarding AFLP patients, reduced antithrombin (AT) activity was seen in all cases tested.[21 - 27] In addition, a gradual decline in AT activity was documented prior to the development of liver dysfunction,[21,28 - 30] suggesting a close relationship between AT deficiency and AFLP.[31]

AT is the most important molecule for anticoagulation of circulating blood. AT activity ranges from 80% to 130% in healthy subjects, whereas acquired AT deficiency is frequently seen in patients admitted to the intensive care unit.[32] A potential role of AT level as a predictor of outcome was suggested and reduced AT activity is associated with increased risk of morbidity and mortality in various clinical conditions outside pregnancy.[33 - 35] In Japan, the measurement of AT activity has become routinely available in most laboratories.[36]

The AT activity decreases gradually in some pregnant women,[21 - 29] and decreased AT activity occurs at higher rates in women with HDP and or multifetal pregnancies.[29,37 - 40] Japanese guidelines for obstetric practice published in 2014 recommended determination of AT activity in women with HDP and or multifetal pregnancies and suspicion of AFLP in women showing AST > 45 IU/L and LDH > 400 IU/L, accompanied by AT activity < 60% in the absence of thrombocytopenia (< 120×10^9/L).[16] However, it has not been clarified whether pregnant women with reduced AT activity are actually at higher risk of liver dysfunction in the absence of thrombocytopenia. This prospective multicenter study was performed to determine whether women with reduced AT activity have higher risk of perinatal liver dysfunction in the absence of thrombocytopenia. If this is the case, clinical introduction of AT activity determination would contribute to improvement of outcome in pregnant women

with insidiously decreased AT activity.

Materials and Methods

This prospective multicenter observational study was conducted after receiving approval from the Institutional Review Board of each participating university hospital (Hokkaido University Hospital [HUH], Jichi Medical University Hospital [JMUH], University Tsukuba Hospital [UTH], Yokohama City University Medical Center [YUMC], and Hamamatsu University Hospital [HmUH] in Japan).

Definition of terms in this study

The antenatal period was defined as 2 weeks prior to delivery. The postnatal period was defined as 1 week after delivery. The perinatal period included the ante- and postnatal periods. Elevated AST level was defined as perinatal AST level > 45 IU/L (reference interval, 13 – 33 IU/L). Elevated LDH level was defined as perinatal LDH level > 400 IU/L (reference interval, 119 – 229 IU/L). Liver dysfunction was diagnosed in women exhibiting elevated AST level (> 45 IU/L) concomitant with elevated LDH level (> 400 IU/L). Hypertension was defined as the occurrence of systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, and gestational hypertension was defined as hypertension occurring on and after gestational week (GW) 20 in the absence of significant proteinuria. Significant proteinuria was defined as a spot-urine protein:creatinine ratio (mg/mg) > 0.27 or > 0.3 g protein loss/24-h urine collection. Preeclampsia was diagnosed in women that developed both hypertension and significant proteinuria on or after GW 20. HDP included gestational hypertension and preeclampsia.

Protocols

The attending physicians at each hospital were able to order laboratory tests, including AT activity, platelet count (PLC), and serum AST/LDH, at their discretion when it was considered helpful for patient care. The prenatal determination of AT activity was performed based on one or more of the following reasons: (1) onset of HDP, (2) appearance of proteinuria with a positive dipstick test result, (3) weight gain ≥ 1.0 kg/week, (4) symptoms including abdominal pain, vaginal bleeding, and convulsions, (5) multifetal pregnancy, and (6) others. All pregnant women fulfilling both of the following conditions were invited to participate in this study: (1) antenatal care given at the five participating university hospitals during the 18-month study period between July 2014 and December 2016, and (2) AT activity was determined antepartum. Women received cares according to the clinical path of each university hospital.

Registration and eligibility for this study

All pregnant women that gave written informed consent to participate in this study were prospectively registered at UMIN Clinical Trials Registration (Number: UMIN000013900**)**
(https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000016206) before completion of their pregnancies. During the study period, there were 5436 and 271 maternities with singleton and twin pregnancies at the five participating hospitals,

respectively. Of these, 630 (12%) and 140 (52%) women carrying singleton and twin pregnancies were registered with data on AT activity, respectively. However, eight women with singleton pregnancies were lost to follow-up. An additional 221 women were excluded from the present analysis because at least one datum of AT activity, PLC, AST, and LDH determined in the antenatal period was unavailable. Finally, 541 women (414 singleton and 127 twin pregnancies) with available antenatal data on all of AT activity, PLC, AST, and LDH were enrolled in this study (Table 1). In women with multiple laboratory data within the same period, the lowest datum was used for AT activity and PLC and the highest datum was used for AST and LDH as representative data for each woman. AT activity was measured using three commercial kits provided by Sekisui Chemical Co., Ltd, Tokyo, Japan (at UTH, YUMC, and HmUH), Symex Co., Ltd, Kobe, Japan (at JMUH) and Daiichi Pure Chemicals Co., Ltd, Tokyo, Japan (at HUH).

Statistical analysis

Data are presented as the median (range). Statistical analyses were performed using the JMP12™ statistical software package (SAS, Cary, NC). The Mann–Whitney U test was used for comparison of medians. Fisher's exact test was used for comparison of categorical variables. Pearson's product–moment correlation coefficient was used to measure linear correlations between two variables. Receiver operating characteristic curve (ROC) was constructed for antenatal AT activity and PLC to assess their ability to differentiate perinatal liver dysfunction. In all analyses, $p < 0.05$ was taken to indicate statistical significance. However, a significant finding regarding a linear correlation between two variables was defined as that meeting both $p < 0.05$ and correlation coefficient (r) > 0.25 or < –0.25.

Results

The leading reasons for blood tests during pregnancy were HDP for women with singleton pregnancies (Table 1).

Of the 541 women included in the study, 22 (4.1%) developed liver dysfunction peripartum; 5 and 17 did so ante- and postpartum, respectively. In the 22 women with perinatal liver dysfunction compared to 519 without perinatal liver dysfunction, GW at registration and delivery were significantly lower, and a significantly greater number of women developed HDP (77% [17/22] vs. 22% [113/519], $p < 0.0001$) and required various medical interventions, including prolonged hospital stay after delivery (Table 2). However, none of the 22 women with liver dysfunction required admission to the intensive care unit and left hospital without sequelae associated with liver dysfunction. Liver dysfunction resolved within three weeks after delivery in all 22 women (see legend for Fig. 1).

Perinatal changes in blood variable levels in women that did and did not develop perinatal liver dysfunction

AT activity, but not PLC level, was already significantly lower at enrollment (at registration), and both AT activity and PLC levels were significantly lower ante- and

postpartum in the 22 women with perinatal liver dysfunction compared to 514 without perinatal liver dysfunction (Fig. 1). In the 541 women, the 5th percentile value was 62% of normal activity level for antenatal AT activity and 118×10^9/L for antenatal PLC. Pregnancy-induced AT deficiency (PIATD) was defined as AT activity ≤ 62% and thrombocytopenia was defined as PLC ≤ 118×10^9/L in this study. Postnatal data on AT activity, PLC, AST, and/or LDH were available in a limited number of women. However, antenatal AT activity was significantly higher in these women with unavailable postnatal laboratory data than in those with available postnatal data. In these women with unavailable postnatal data on AST and LDH, we assumed that they did not have elevated levels of AST and LDH postpartum.

Perinatal frequencies of the elevated levels of AST and LDH and liver dysfunction increased with decreasing antenatal AT activity as well as antenatal PLC level (Fig. 2).

Associations of the lowest perinatal AT activity and PLC levels with AST and LDH levels (Fig. 3)

Both the lowest perinatal AT activity and the lowest perinatal PLC exhibited significant weak negative correlations with the highest LDH level, but not the highest AST level (Fig. 3). The lowest perinatal AT activity also exhibited a significant and weak positive correlation with the lowest PLC.

Relationships between antenatal PIATD, antenatal thrombocytopenia, perinatal liver dysfunction, and HDP (Fig. 4)

HDP, antenatal PIATD, antenatal thrombocytopenia, and perinatal liver dysfunction occurred in 130 (24%), 28 (5.2%), 29 (5.4%), and 22 (4.1%) of the 541 women, respectively (Fig. 4). The relative risk (RR with 95% confidence interval [95%CI]) of perinatal liver dysfunction was 10.7 (4.04 – 28.3) (13% [17/130] vs. 1.2% [5/411], respectively) for women with HDP vs. those without HDP. The risk of perinatal liver dysfunction was similar between three groups divided by the presence or absence of PIATD and thrombocytopenia: 20% (4/20) for women with antenatal PIATD, but not with antenatal thrombocytopenia; 19% (4/21) for women with antenatal thrombocytopenia, but not antenatal PIATD; and 13% (1/8) for women with both PIATD and thrombocytopenia (Fig. 4). The RR of 5.79 (2.16 – 15.5) (20% [4/20] vs. 3.5% [18/521], respectively) for women with antenatal PIATD, but not antenatal thrombocytopenia vs. the remaining 521 women, was comparable to that of 5.50 (2.04 – 14.8) (19% [4/21] vs. 3.5% [18/520], respectively) for women with antenatal thrombocytopenia, but not with antenatal PIATD vs. the remaining 520. Thus, antenatal PIATD was a risk factor for perinatal liver dysfunction even in the absence of antenatal thrombocytopenia.

Of the 22 women with liver dysfunction, eight (36%) experienced PIATD perinatally and five did not experience thrombocytopenia at all throughout perinatal period (see legend for Fig. 4). Finally, these five women with perinatal PIATD but not thrombocytopenia were clinically suspected as having AFLP, showing lowest perinatal AT activity of 45 (41 – 62)%, lowest perinatal PLC of 164 (127 – 235)$\times10^9$/L, and

highest perinatal AST/LDH levels of 158 (46 – 346)/480 (401 – 551) IU/L based on the Japanese guidelines.[16] Three of the five with suspected AFLP were twin pregnancies. Another 14 women with perinatal thrombocytopenia were diagnosed with HELLP syndrome regardless of AT activity and showed the lowest perinatal AT activity of 71 (52 – 108)%, lowest perinatal PLC of 79 (28 – 118)×10^9/L, and highest perinatal AST/LDH levels of 204 (51 – 1825)/561 (413 – 2574) IU/L based on the Japanese guidelines.[16] All of the 14 with HELLP syndrome were singleton pregnancies.

Women with twin pregnancies accounted for 54% (15/28) of all women with antenatal PIATD and 41% (12/29) of all women with antenatal thrombocytopenia (see legend for Fig. 4). Thus, women with twin pregnancies were significantly more likely to develop PIATD (12% [15/127] vs. 3.1% [13/414], respectively, $p = 0.0004$) and thrombocytopenia (9.4% [12/127] vs. 1.1% [17/414], respectively, $p = 0.0214$) compared to women with singleton pregnancies.

***Screening characteristics of antenatal AT activity and PLC for prediction of perinatal liver dysfunction** (Fig. 5)*

The abilities of antenatal AT activity and PLC for prediction of perinatal liver dysfunction were analyzed using ROC (Fig. 5). The areas under the curve (AUC) were 0.677 for antenatal AT activity and 0.688 for antenatal PLC. The best cut-off of antenatal AT activity, i.e., 77%, suggested by ROC yielded a sensitivity of 59% (13/22), specificity of 73% (381/519), positive predictive value (PPV) of 8.6% (13/151), and negative predictive value (NPV) of 98% (381/390). Corresponding figures for the best cut-off of antenatal PLC, i.e., 139×10^9/L, yielded sensitivity of 41% (9/22), specificity of 90% (465/519), PPV of 14% (9/63), and NPV of 97% (465/478). Thus, screening characteristics of antenatal AT activity was comparable to those of antenatal PLC for prediction of perinatal liver dysfunction. Combined use of AT activity and PLC increased sensitivity to 73% (16/22) with PPV of 9.2% (16/173) when a positive result on either test result was taken as positive.

Discussion

In this study, the risk of perinatal liver dysfunction was approximately 6-fold higher for women with antenatal PIATD, but not antenatal thrombocytopenia, compared to those with counterpart characteristics. Eight of 22 women (36%) with liver dysfunction showed PIATD during the perinatal period, and 5 of them (23%) lacked thrombocytopenia. Based on the assumption that these 5 women suffered from AFLP, the results of this study were consistent with a previous study by Knight *et al.*[3] in which 24 (52%) of 46 women diagnosed with AFLP had coagulopathy in the absence of thrombocytopenia (defined as PLC < 100×10^9/L). Patients with coagulopathy, such as DIC, are likely to have reduced AT activity and thrombocytopenia,[33 – 35] and reduced AT activity, ranging from 0.0% to 69%, was seen in all AFLP patients tested.[21 – 27,31] We speculated that PIATD may have been found if AT activity was tested in a considerable number of AFLP patients reported to date with unknown AT activity.

The risk of liver dysfunction increased with decreasing AT activity (Fig. 2), confirming the results of retrospective studies.[29,41] This suggested that use of AT activity was helpful for identifying women at risk of liver dysfunction. Indeed, an antenatal AT activity cut-off of 77% suggested by ROC analysis succeeded in detecting approximately 60% of women that developed liver dysfunction peripartum. Use of antenatal PLC was also helpful to detect women at risk of liver dysfunction. However, a considerable number of women developed perinatal liver dysfunction in the absence of thrombocytopenia, and the use of AT activity in addition to PLC improved detection rate to 73% (16/22) of perinatal liver dysfunction in this study.

The frequency of PIATD was significantly higher for women carrying twins than singletons in this study, consistent with the results of earlier studies[37 – 40]: the prevalence rate of PIATD (defined as perinatal ≤ AT 65%) was 0.7% (2/300) – 2.3% (33/1412) among women with uncomplicated singleton pregnancies[39,40] and the degree of antenatal decline in AT activity was consistently greater in twin than in singleton pregnancies.[37,38] This explained why twin pregnancy is a consistent and prominent risk factor for AFLP; twin pregnancies accounted for 14% (19/140),[2] 18% (10/57),[3] 22% (4/18),[42] 22% (4/18),[5] and 29% (4/14)[22] of AFLP cases, although twin pregnancy accounts for only 1.0% – 2.0% of all pregnancies in most countries.

We were concerned with liver dysfunction associated with PIATD and thrombocytopenia because such liver dysfunction is considered to result in a propensity for coagulopathy and elevated LDH level, as seen in patients with HELLP syndrome and AFLP.[7,8] Therefore, we defined liver dysfunction as elevated levels of both AST and LDH in this study. It was interesting to note that both AT activity and PLC levels were relatively well correlated with LDH levels rather than AST levels (Fig. 2, Fig. 3). Therefore, it may have been adequate to include LDH level in the definition of liver dysfunction in this study. In addition, the number of women with liver dysfunction was not overestimated by this definition; in a prospective study in the UK,[1] perinatal liver dysfunction was seen in 3.2% of 4377 deliveries, and HDP was a prominent risk factor for liver dysfunction, which was 4.1% (22/541) in our selected population containing a much higher number of women with HDP (24%) than the general population.

The mechanism(s) underlying the link between PIATD and liver dysfunction remains unknown. As AT is produced in the liver, PIATD may occur as a result of liver dysfunction. However, a direct causal relationship is unlikely. As shown in this study, AT activity levels were significantly positively correlated with PLC, suggesting that hemostasis, coagulation, and fibrinolysis were enhanced in these patients with liver dysfunction associated with PIATD and or thrombocytopenia. A study by Van Dam *et al.*[43] examining 18 patients diagnosed with HELLP syndrome indicated mean AT activity and PLC of 60% and 83×10^9/L, respectively, on admission to hospital, which decreased to 56% and 65×10^9/L, respectively, at delivery. Enhanced coagulation-fibrinolysis and vascular hyperpermeability were suggested in PIATD women.[40] The former causes hyperconsumption of AT leading to reduced AT activity,[37] while the latter may cause a decrease in circulating plasma volume. Decreased

circulating plasma volume can cause inadequate blood perfusion to the liver leading to liver dysfunction, as seen in women with HELLP syndrome.[44 – 45] AT also escapes from the blood into the interstitial space in the presence of enhanced vascular permeability.[46] In an animal model, a protective role of AT against liver dysfunction due to its anticoagulant and anti-inflammatory action is suggested.[47] Therefore, we speculated that dysfunctional vascular endothelium associated with PIATD mediated liver dysfunction.

This study had two major limitations. First, not all of the women underwent postnatal laboratory tests. We assumed that these women with unavailable postnatal data on AST and LDH did not have liver dysfunction based on our previous findings that none developed perinatal liver dysfunction in consecutive 127 women with perinatal AT activity > 65%.[41] Second, the present cohort included larger numbers of women with HDP and twin pregnancies than the general population, and therefore did not represent the general population.

Liver dysfunction associated with reduced AT activity and/or thrombocytopenia, such as AFLP and HELLP syndrome, are life-threatening conditions. This study emphasized that antenatal AT activity could predict liver dysfunction not accompanied by thrombocytopenia and use of PLC alone was insufficient to predict serious liver dysfunction associated with reduced AT activity, such as AFLP. Combined use of AT activity and PLC may contribute to increased safety of pregnant women.

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Disclosure
All authors have no conflicts of interest.

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Figure legends

Figure 1 Changes in blood variables in women with and without liver dysfunction

Closed and open circles indicate women with and without perinatal liver dysfunction, respectively. *, $p < 0.05$ vs. women without liver dysfunction. In the 22 and 519 women with vs. without perinatal dysfunction, antenatal data were obtained 2 (0 – 14) vs. 1 (0 – 14) days prior to delivery, $p = 0.7351$, respectively, and postnatal data were obtained 1 (1 – 3) vs. 1 (1 – 6) days after delivery, $p = 0.7602$, respectively. Liver dysfunction resolved within three weeks after childbirth in all 22 women; AST level was 24 (13 – 38) IU/L on postpartum day (PPD) 7 (2 – 21), LDH level was 274 (159 – 379) IU/L on PPD 7 (4 – 21), AT activity level was 92 (76 – 118) % on PPD 6 (1 – 7), and PLC was 286 (92 – 534) $\times 10^9$/L on PPD 6 (1 – 21) in the 22 women. In the 541 women, antenatal median (5^{th} – 95^{th}) value was 85 (62 – 110)% for AT activity, 202 (118 – 315)$\times 10^9$/L for PLC, 18 (11 – 40) IU/L for AST, and 186 (138 – 301) IU/L for LDH. In the 519 women without perinatal liver dysfunction, postnatal data on AT activity were unknown in 248 women of whom 186 and 187 postnatal AST and LDH were unknown. The median antenatal AT activity and PLC were 87 vs. 84%, $p = 0.0007$, respectively and 201 vs. 205$\times 10^9$/L, $p = 0.5382$, respectively, for 248 women with unknown postnatal AT activity vs. 271 women with postnatal data on AT activity.

Figure 2 Frequency of perinatal laboratory abnormalities and perinatal liver dysfunction according to antenatal AT activity and platelet count

*, $p < 0.05$ vs. respective frequency in women with AT activity ≥ 85% or ≥ PLC 180$\times 10^9$/L. Frequency of liver dysfunction appeared to increase with decreasing antenatal AT activity and/or PLC: frequency of liver dysfunction was 11.1% (6/54), 7.7% (6/78), 2.9% (4/140), and 2.2% (6/269) for women with antenatal AT activity of ≤ 66%, 67 – 75%, 76 – 85%, and ≥ 86%, respectively, and 14.6% (8/55), 2.6% (2/76), 4.3% (6/140), and 2.2% (6/270) for women with PLC of ≤ 136$\times 10^9$/L, 137 – 164 $\times$ 10^9/L, 165 – 202 $\times$ 10^9/L, and ≥ 203 $\times$ 10^9/L, respectively.

Figure 3 Associations of the lowest perinatal AT activity and PLC levels with the highest perinatal AST and LDH levels

In each woman participating in this study, data of the lowest perinatal AT activity and PLC and those of the highest perinatal AST and LDH were used as representative data for these analyses.

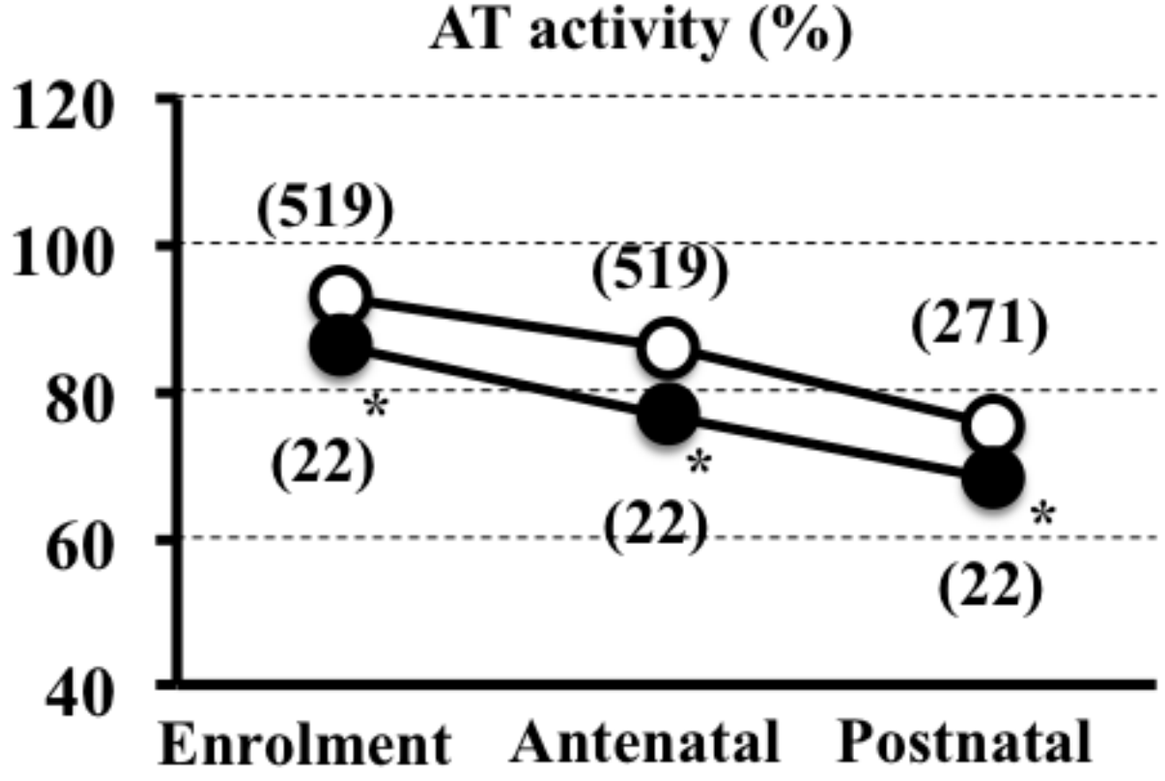
Fig. 4 Relationship between HDP, antenatal PIATD, antenatal thrombocytopenia, and perinatal liver dysfunction

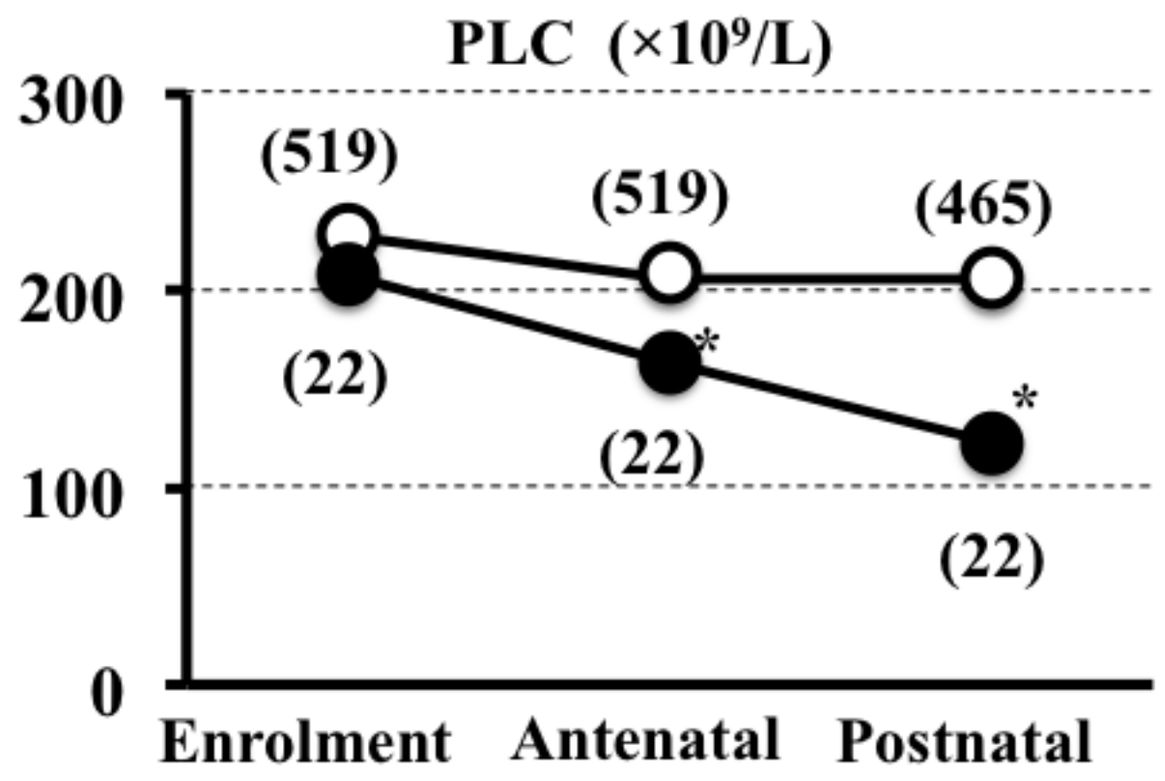
Numerals in circles indicate numbers of women. Women with twin pregnancies accounted for 54% (15/28) of all women with PIATD and 41% (12/29) of all women with thrombocytopenia. Of all 22 women with perinatal liver dysfunction (17 and 5

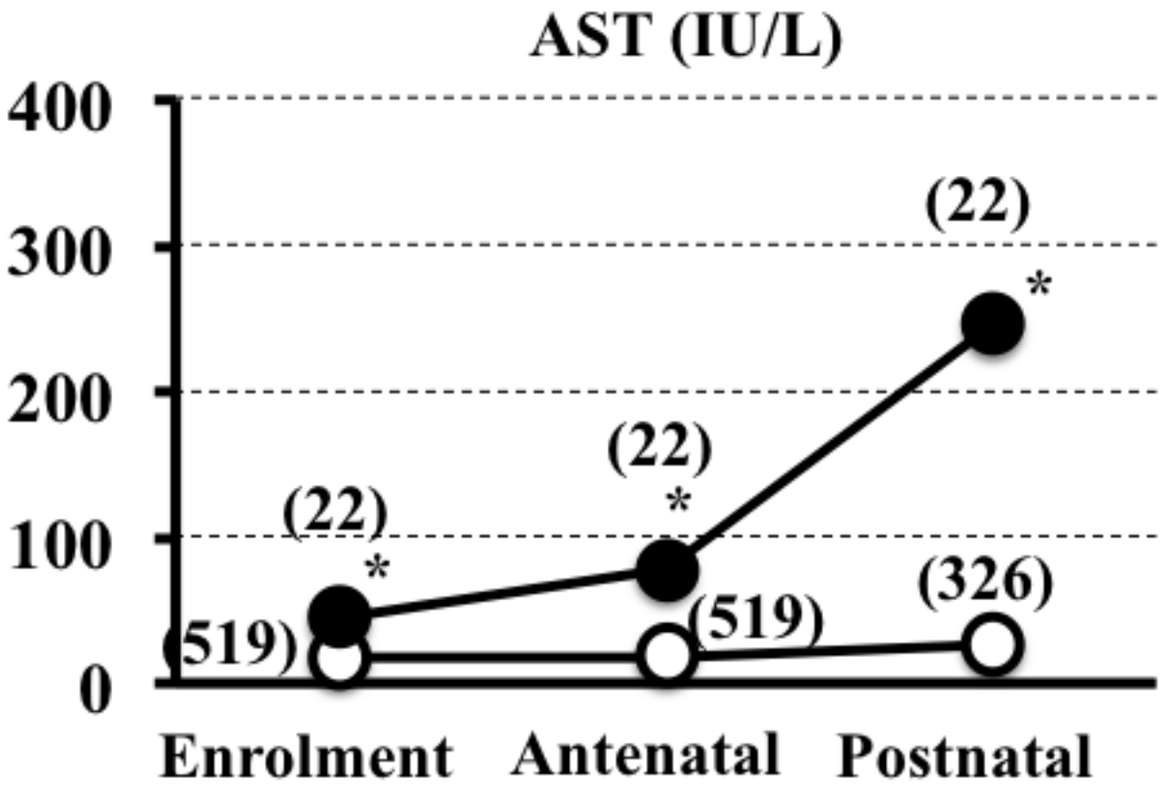
with and without HDP, respectively), 4, 4, 1, and 13 women showed PIATD (AT activity ≤ 62%) alone, thrombocytopenia (PLC ≤ 118×10^9/L) alone, both PIATD and thrombocytopenia, and neither PIATD nor thrombocytopenia, respectively, antepartum (Fig. 4), while 4, 10, 2, and 6 women, respectively, did so during the postpartum period (data not shown). Finally, 5, 11, 3, and 3 women experienced PIATD alone, thrombocytopenia alone, both PIATD and thrombocytopenia, neither PIATD nor thrombocytopenia, respectively, peripartum.

Figure 5 Receiver operating characteristic curves of antenatal AT activity and platelet count for prediction of perinatal liver dysfunction

Figure 1


AT activity (%)
120
100
80
60
40
(519)
(519)
(271)
(22)
(22)
(22)
*
*
*
Enrolment
Antenatal
Postnatal


PLC (×10⁹/L)
300
200
100
0
(519)
(519)
(465)
(22)
(22)
(22)
*
*
Enrolment
Antenatal
Postnatal


AST (IU/L)
400
300
200
100
0
(22)
(22)
(22)
(519)
(519)
(326)
*
*
*
Enrolment
Antenatal
Postnatal

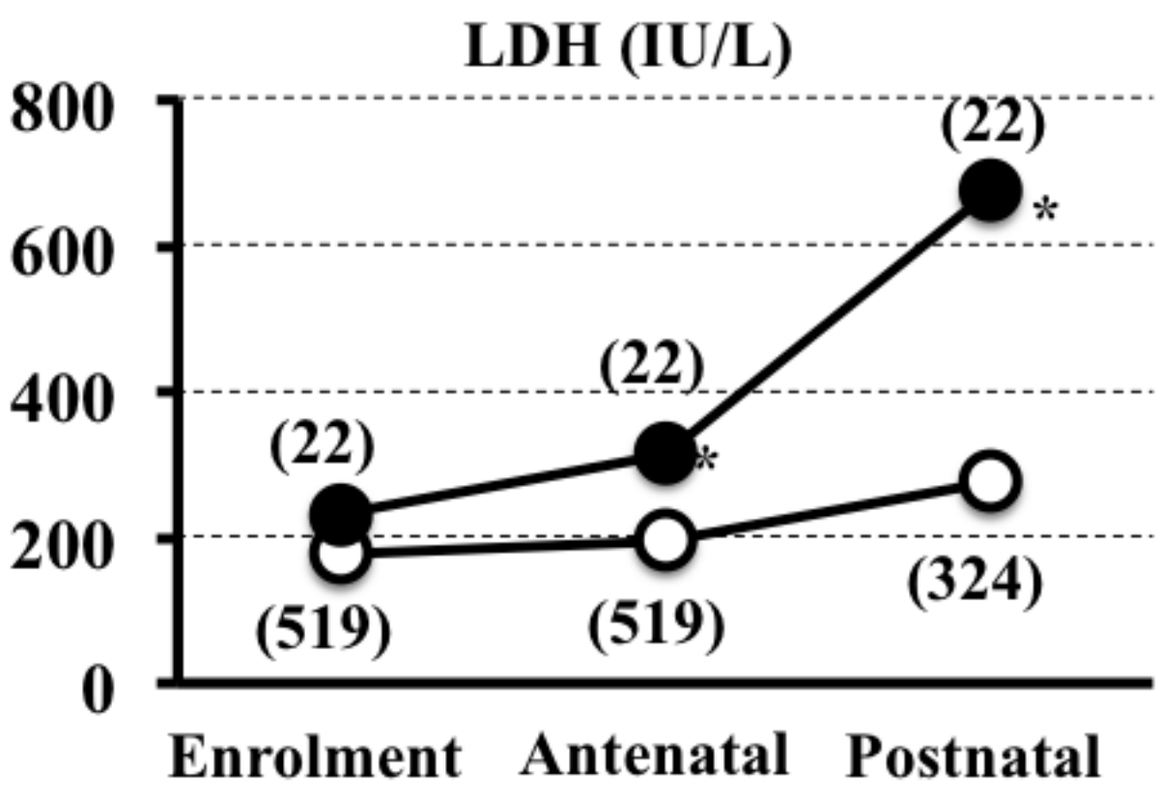

LDH (IU/L)
800
600
400
200
0
(22)
(22)
(22)
(519)
(519)
(324)
*
*
Enrolment
Antenatal
Postnatal

Figure 2

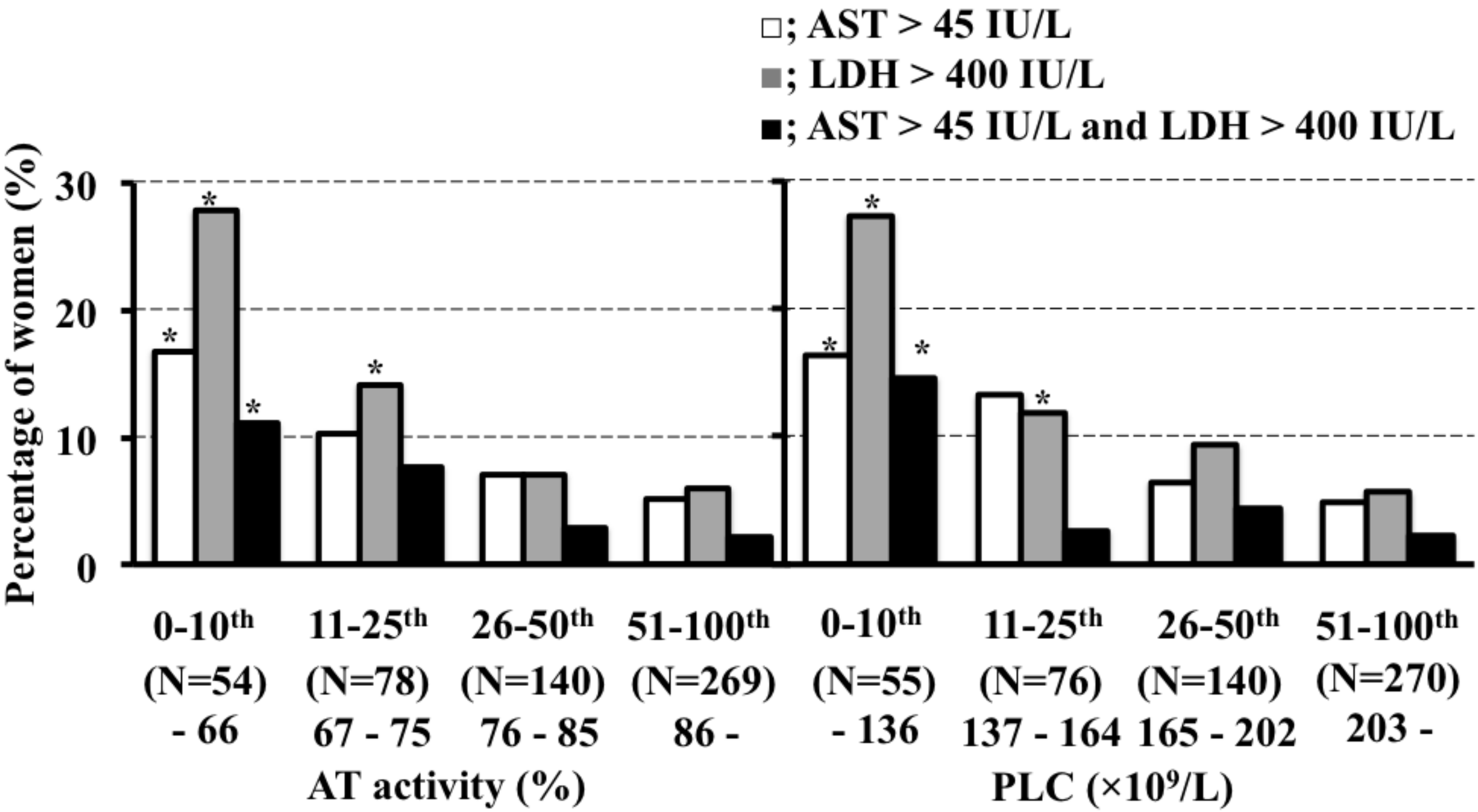

□; AST > 45 IU/L
■; LDH > 400 IU/L
■; AST > 45 IU/L and LDH > 400 IU/L
Percentage of women (%)
30
20
10
0
*
0-10th (N=54) - 66
11-25th (N=78) 67 - 75
26-50th (N=140) 76 - 85
51-100th (N=269) 86 -
AT activity (%)
0-10th (N=55) - 136
11-25th (N=76) 137 - 164
26-50th (N=140) 165 - 202
51-100th (N=270) 203 -
PLC (×10⁹/L)

Figure 3

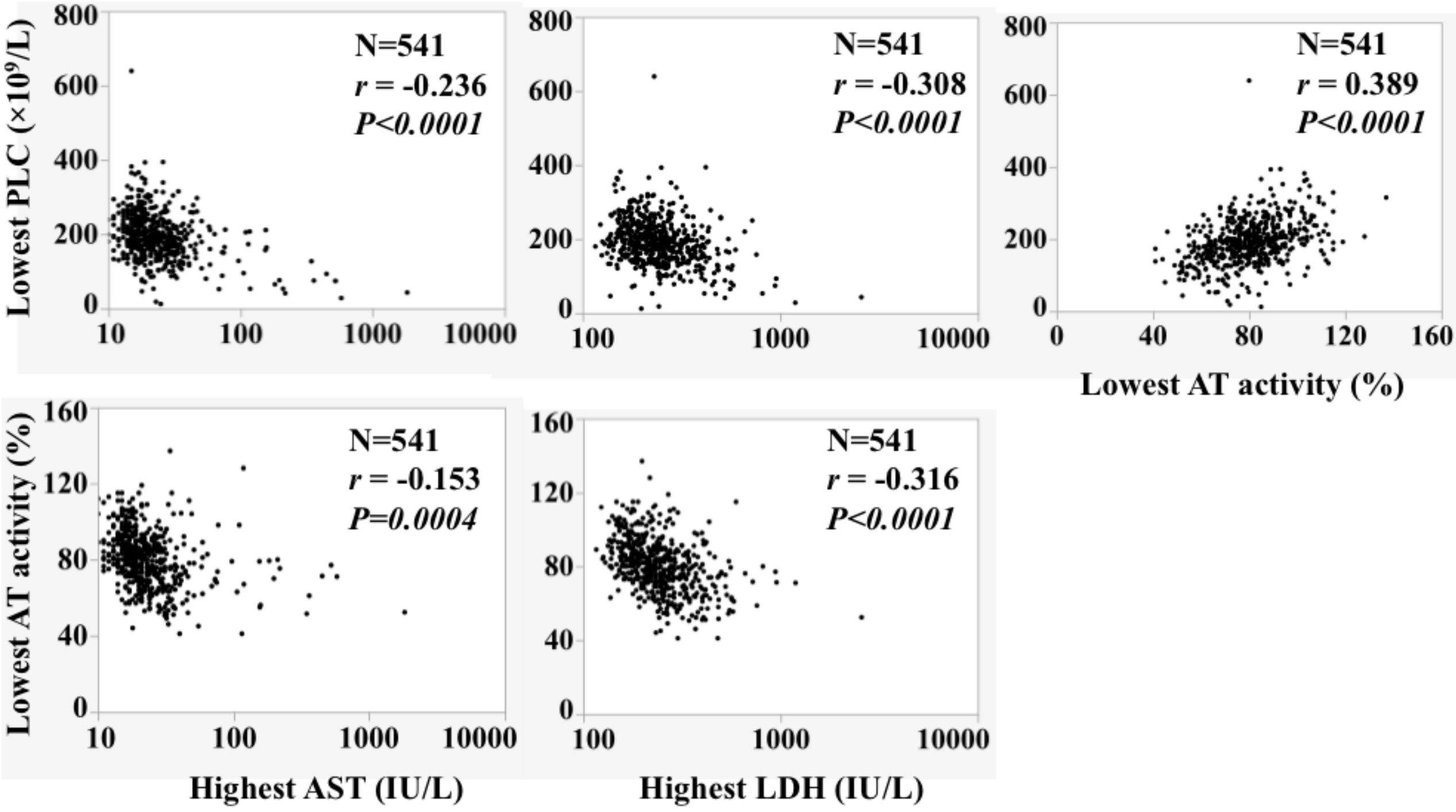

Lowest PLC (×10⁹/L)
800
600
400
200
0
10
100
1000
10000
N=541
r = -0.236
P<0.0001
N=541
r = -0.308
P<0.0001
0
40
80
120
160
N=541
r = 0.389
P<0.0001
Lowest AT activity (%)
Lowest AT activity (%)
N=541
r = -0.153
P=0.0004
N=541
r = -0.316
P<0.0001
Highest AST (IU/L)
Highest LDH (IU/L)

Figure 4

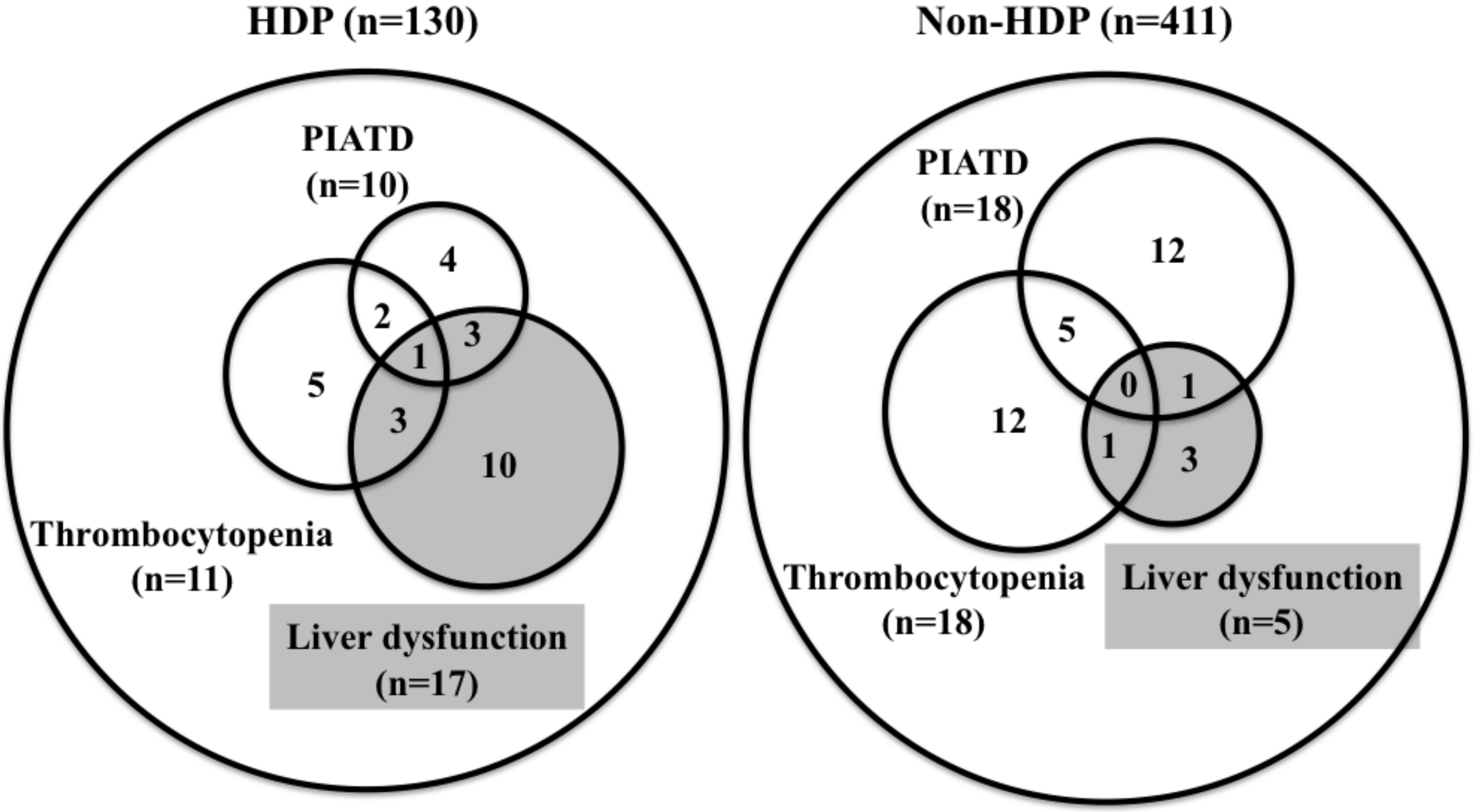

HDP (n=130)
PIATD
(n=10)
4
2
3
1
5
3
10
Thrombocytopenia
(n=11)
Liver dysfunction
(n=17)
Non-HDP (n=411)
PIATD
(n=18)
12
5
0
1
12
1
3
Thrombocytopenia
(n=18)
Liver dysfunction
(n=5)

Figure 5

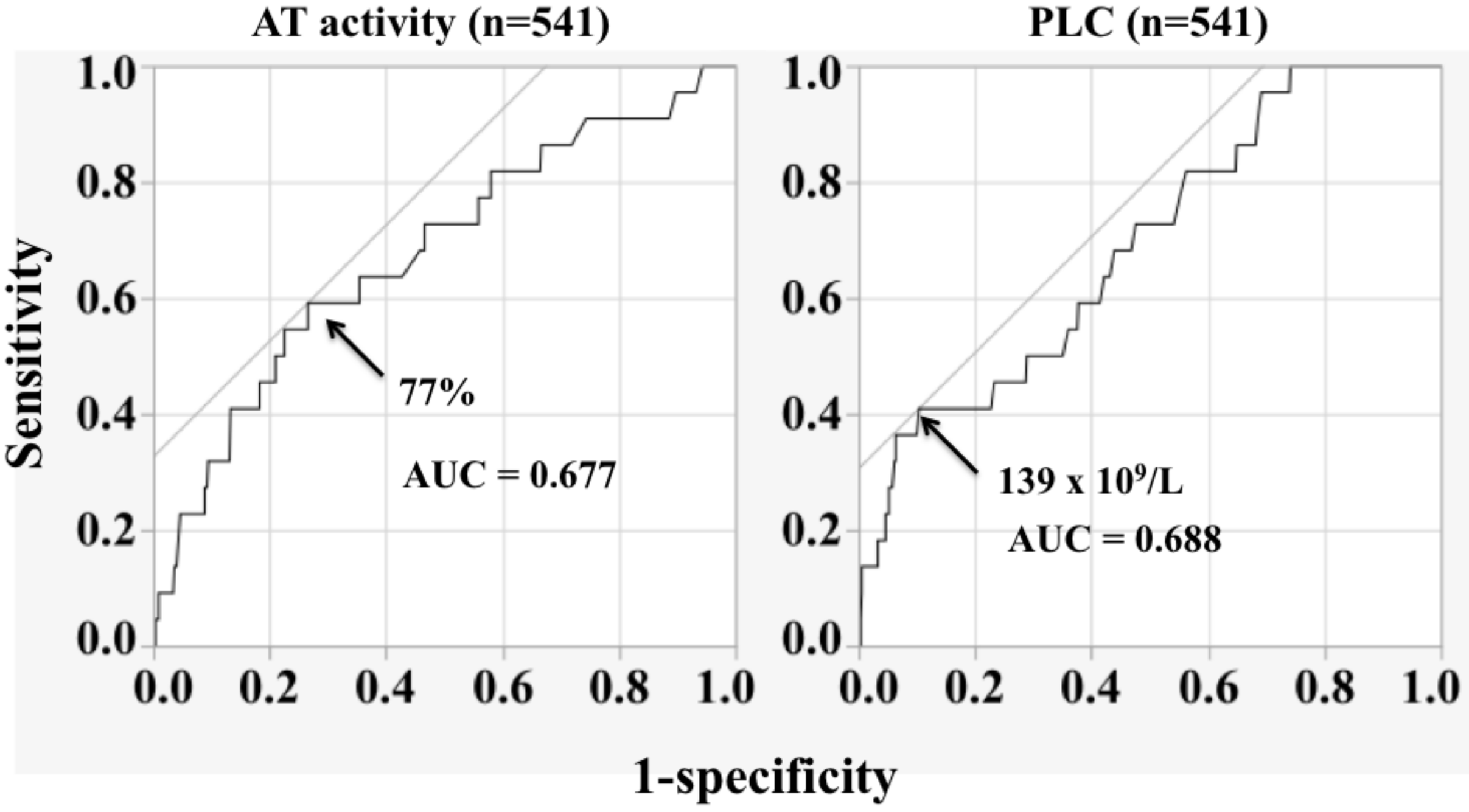

AT activity (n=541)
PLC (n=541)
Sensitivity
1.0
0.8
0.6
0.4
0.2
0.0
77%
AUC = 0.677
139 x 10⁹/L
AUC = 0.688
0.0
0.2
0.4
0.6
0.8
1.0
1-specificity

Table 1 Demographic characteristics of 541 subjects

	Overall	Singleton	Twin
Number of women	541	414	127
Age (years)	34 [18–53]	34 [18–45]	33 [21–53]*
Height (m)	1.58 [1.42–1.77]	1.58 [142 - 177]	1.58 [145 - 172]
Nulliparity	296 (54.7%)	219 (52.9%)	77 (60.6%)
Prior caesarean section	76 (14.0%)	68 (16.4%)	8 (6.3%)*
Prior HDP	20 (3.7%)	19 (4.6%)	1 (0.8%)
Pre-pregnancy weight (kg)	52.7 [34.5–106.0]	53.0 [34.5–106.0]	50.0 [36.0–93.0] *
Body mass index (kg/m^2)	20.7 [14.6–45.0]	20.8 [14.6–45.0]	20.3 [16.2–36.3] *
Gestational week at registration	34.7 [20.0–41.4]	35.3 [20.0–41.4]	32.4 [22.6–36.4] *
Reasons for blood tests			
Hypertension	88 (16.3%)	83 (20.1%)	5 (3.9%)*
Proteinuria	42 (7.8%)	36 (8.7%)	6 (4.7%)
Body weight gain $\geq$1.0 kg/week	7 (1.3%)	7 (1.7%)	0 (0.0%)
Symptoms	12 (2.2%)	11 (2.7%)	1 (0.8%)
Twin pregnancy	123 (22.7%)	0 (0.0%)	123 (96.9%)*
Others	329 (60.8%)	314 (75.9%)	15 (11.8%)*
Gestational week at delivery	37.6 [22.9–41.7]	38.0 [22.9–41.7]	37.0 [23.0–40.0] *

Data are presented as the median [range] or number (percentage). *, $p < 0.05$ vs. singletons; HDP, hypertensive disorders of pregnancy; NICU, neonatal intensive care unit.

Table 2 Demographic characteristics and clinical outcomes of 22 women with liver dysfunction vs. 519 women without liver dysfunction

	Perinatal liver dysfunction		
	Yes	No	*p*-value
Number of women	22*	519	
Age (years)	36 [27–42]	34 [18–53]	0.2407
Height (m)	1.56 [142 - 164]	1.58 [142 - 177]	0.0488
Nulliparity	14 (63.6%)	282 (54.3%)	0.5130
Pre-pregnancy weight (kg)	53.5 [37.0–76.0]	52.5 [34.5–106]	0.7991
Body mass index (kg/m^2)	21.5 [14.6–32.9]	20.7 [14.8–45.0]	0.3119
Twin pregnancy	4 (18.2%)	123 (23.7%)	0.7973
Gestational week (GW) at registration*	31.1 [24.4–40.4]	34.9 [20.0–41.4]	< 0.0001
HDP	17 (77.3%)	113 (21.8%)	< 0.0001
Gestational hypertension	3 (13.6%)	58 (11.2%)	0.7276
Preeclampsia	14 (63.6%)	55 (10.6%)	< 0.0001
Medical intervention			
Antenatal hospital stay ≥ 7 days	16 (72.7%)	261 (50.3%)	0.0492
Use of antihypertensives	14 (63.6%)	75 (14.5%)	< 0.0001
Induction of labor	1 (4.5%)	74 (14.3%)	0.3408
Caesarean section	21 (95.5%)	341 (65.7%)	0.0021
Gestational week (GW) at delivery*	33.9 [26.4–40.4]	37.6 [22.9–41.7]	< 0.0001
< 37	19 (86.4%)	145 (27.9%)	< 0.0001
Caesarean section for birth at GW < 37	18/19 (94.7%)	124/145 (85.5%)	0.4740
Postpartum day at hospital discharge	7 [6–17]	6 [2–32]	0.0219
Infants (number)	26	642	
Birthweight (g)	1604 [676–2962]	2554 [315–4042]	< 0.0001
Apgar score < 8 at 5 min	3 (11.5%)	55 (8.6%)	0.4865
Admission to NICU	23 (88.4%)	208 (32.4%)	< 0.0001

Data are presented as the median (range) or number (percentage). HDP, hypertensive disorders of pregnancy; NICU, neonatal intensive care unit. *, Liver dysfunction occurred ante- (within 2 weeks prior to delivery) and postpartum (within 1 week after delivery) in 5 and 17 women and GW at registration was 31.4 (24.4–40.4), and 32.0 (24.4–35.3), and GW at delivery was 31.7 (27.6–40.4) and 34.4 (26.4–37.1) for the former and latter, respectively.