Original Article - Robotics/Laparoscopy

Investig Clin Urol 2020;61:277-283.
https://doi.org/10.4111/icu.2020.61.3.277
pISSN 2466-0493 • eISSN 2466-054X

INVESTIGATIVE AND CLINICAL UROLOGY
ICUROLOGY

Predictive factors and radiological findings of adrenohepatic adhesion during laparoscopic adrenalectomy

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Purpose: This retrospective study aimed to identify predictive factors and imaging features of adrenohepatic adhesion found during laparoscopic right adrenalectomy.

Materials and Methods: Altogether, 77 patients underwent laparoscopic right adrenalectomy between January 2005 and December 2018. Adrenohepatic adhesion was defined as strict adhesion that required either partial adrenalectomy with coagulation of residual tissue or partial hepatectomy to accomplish complete resection. We assessed their surgical video records to determine if adrenohepatic adhesion was present. Age, sex, body mass index, tumor size, tumor diagnosis and radiological findings (attachment between the liver and the adrenal gland, diameters of the right and left adrenal veins and its ratio) were evaluated as preoperative variables.

Results: Adrenohepatic adhesion was present in 11 of the 77 patients (14.3%). Age, sex, and body mass index were not statistically significant factors. Tumor size was significantly small in adhesion group (14.2 mm vs. 25.9 mm, p=0.02). Attachment to the liver and adrenal gland was frequently seen regardless of the adhesion. The mean right/left adrenal veins diameters ratio was significantly lower in the adhesion group (0.8 vs. 1.1, p=0.01). Multivariate logistic regression analysis demonstrated the right/left adrenal veins diameters ratio was the only significant predictor of adhesion. The sensitivity, specificity, negative predictive value and positive predictive value were 0.82, 0.76, 0.43, and 0.95 respectively when the optimal cutoff value for the ratio was 0.9 (area under the curve, 0.75; 95% confidence interval, 0.60–0.90).

Conclusions: The right/left adrenal veins diameters ratio was possible predictor of adrenohepatic adhesion.

Keywords: Adrenalectomy; Adrenal glands; Laparoscopy; Radiography; Tissue adhesions

INTRODUCTION

Adrenohepatic adhesion (AHA) refers to tight adhesion between the lower surface of the liver and the adrenal gland (Fig. 1) [1]. Sugimoto et al. [2] reported that AHA was found in approximately 10% patients during laparoscopic adrenalectomy and was the main reason for incomplete resection of the adrenal gland. Histologically, AHA is a party-wall

Received: 19 July, 2019 • **Accepted:** 3 December, 2019
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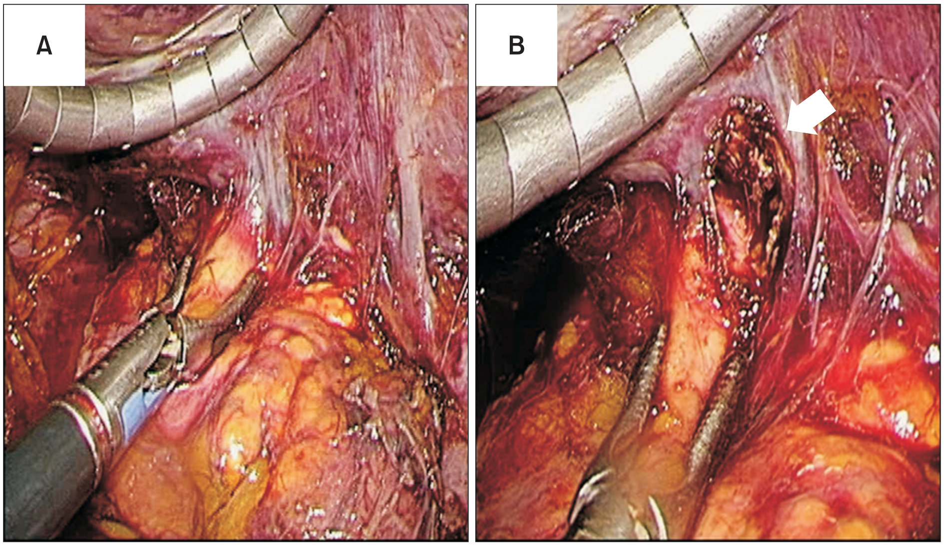

Fig. 1. (A) Adrenohepatic adhesion during right laparoscopic adrenalectomy. Tight adhesion between the lower surface of the liver and the adrenal gland was observed. (B) Liver parenchyma (white arrow) was exposed after separating those tissues.

sharing of the liver and the adrenal gland capsule caused by failure of local differentiation into fetal fat cell (Fig. 2) [1]. Separation of AHA in such cases would increase the risk of liver injury, and the residual tissue could be a site of recurrence [3,4]. Although the importance of being aware of the possibility of AHA in patients undergoing right adrenalectomy has been noted [5-7], its predictive factors and preoperative imaging features have not been elucidated. The aim of this study was to identify the predictive factors and imaging features of AHA.

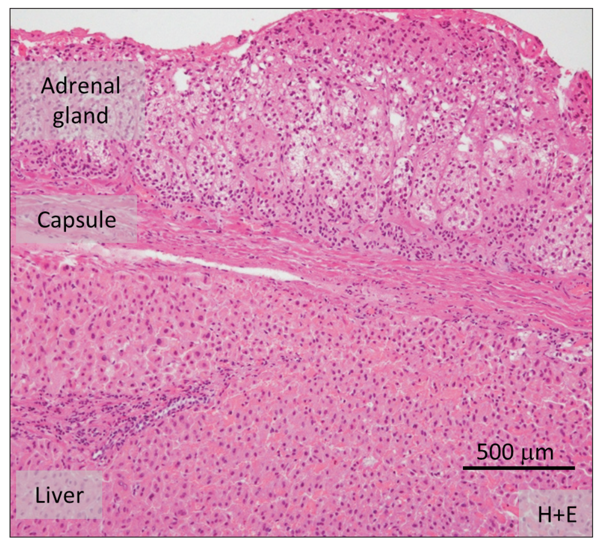

Fig. 2. Histopathological image of adrenohepatic adhesion. There is no physical separation of these organs by interposition of fat cells.

MATERIALS AND METHODS

The review board of Kyoto Medical Center approved this study in which we retrospectively analyzed 77 patients who underwent laparoscopic right adrenalectomy for benign adrenal tumor from January 2005 to December 2018 (approval number: 18-054). Indication of laparoscopic adrenalectomy includes benign functional tumor and nonfunctioning adenoma >40 mm. If malignancy was highly suspected, we recommended open surgery. Patients who underwent open adrenalectomy or planned partial adrenalectomy case were not included. The parameters evaluated included age, sex, body mass index (BMI), history of abdominal surgery, diagnosis of a tumor; non-functioning, primary aldosteronism (PA), Cushing's syndrome (CS), pheochromocytoma, and tumor size. Previously reported radiological findings [8] (attachment between the liver and the adrenal gland, diameters of the right and left adrenal veins and the right/left diameters ratio) were evaluated. The operative time, estimated blood loss, intraoperative complications and postoperative complications were also assessed.

All laparoscopic right adrenalectomies were performed using a four- or five-port, transperitoneal approach. At first, we divided the triangular ligament and retracted the liver. We incised the peritoneum along the inferior vena cava (IVC), and exposed IVC and renal vein. Posterior and inferior side of adrenal gland was dissected from posterior abdominal wall and upper side of renal surface. We dissected upward between IVC and adrenal gland until adrenal central vein was identified. Adrenal central vein was divided with vessel clips or sealed with ultrasonic devices. Finally we separated the adrenal gland from the liver and completed mobilization. In case of adhesion between the adrenal gland and the liver, partial adrenalectomy with coagulation of residual tissue or combined resection of hepatic capsule was

https://doi.org/10.4111/icu.2020.61.3.277

performed according to tumor characteristics.

Multiple surgeons, mainly under training, performed the procedure. In case of difficult dissection between the adrenal gland and other organs or intraoperative complication, the operator was changed to supervisor.

AHA was defined as the adhesion which met both following 2 criteria: 1) either partial adrenalectomy or partial hepatectomy was performed to accomplish complete resection; 2) adhesiolysis time >30 minutes to complete separation between the adrenal gland and the liver after division of adrenal vein. The author (K.I.) independently assessed surgical procedures and adhesiolysis time for all of the nonedited video records.

We gathered the radiological data from the patients' preoperative contrast-enhanced or non-enhanced computed tomography (CT) scans with a range of 1 to 5 mm slice thickness. All radiographic data were collected by one of the authors (H.A.) in an independent, blinded fashion regarding the patients' characteristics and the surgical records. The adrenal gland was defined as "attached" to the liver when there was no fat between the liver and the right adrenal gland (Fig. 3A). The maximum diameters of the right and left adrenal veins were obtained from axial CT images (Fig. 3B, C). The right/left adrenal veins' diameters ratio was calculated only when both right and left veins were measurable. Only axial images were interpreted to avoid interpretation bias. Sagittal or frontal CT images had been discarded except for recent cases, and image quality significantly degraded after reconstruction.

All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphic user interface for R (The R Foundation for Statistical Computing, version 2.13.0; Vienna, Austria) [9]. It is also a modified version of R commander (version 1.6-3), which includes statistical functions for biostatistics.

Student t-test, Mann–Whitney U test and Fisher exact test were used for comparisons of parametric, nonparametric and categorical variables, respectively. Multivariate logistic regression was used to analyze possible predictors of AHA. Receiver operating characteristic curves and the area under the curve (AUC) analysis were performed and the optimal cut-off point to predict AHA was determined by the Youden index (max [sensitivity+specificity-1]). All tests were two-sided, with $p<0.05$ considered to indicate statistical significance.

RESULTS

AHA was seen in 11 of 77 patients (14.3%). The incomplete resection with coagulation of remained tissue was observed in 8 patients (10.4%), and partial hepatectomy was performed for 3 (3.9%). The clinical characteristics and surgical outcomes of the patients with and without AHA are shown in Table 1. Age, sex, BMI and history of abdominal surgery were not statistically different between the two groups. Overall, 19.3% of patients with PA and 17.6% with pheochromocytoma had AHA, whereas 4.5% of the patients with CS had AHA. Tumor size was significantly small in adhesion group (14.2 mm vs. 25.9 mm, $p=0.02$). The adhesion group had significantly higher rate of liver injury (45.5% vs. 3.0%, $p<0.01$). The operative time, estimated blood loss, other intraoperative complications and postoperative complications were not statistically different between the two groups.

Radiographic features of the patients with and without AHA are shown in Table 2. Radiography showed attachment of the liver and adrenal gland in 63.6% of patients with adhesion and in 59.1% without adhesion. The diameters of the adrenal veins were measurable in 11 (100.0%) patients in the adhesion group and 49 (74.2%) in the non-adhesion group. The median right/left adrenal veins diameters ratio (0.8 vs. 1.1, $p=0.01$) were significantly small in the AHA group. The box and dot plot of right/left adrenal veins diameters ratio are shown in Supplementary Fig. 1.

Multivariate logistic analysis demonstrated the right/left

Fig. 3. (A) "Attached" adrenal gland. No fat was interposed between the liver and the adrenal gland (arrows). (B, C) Adrenal glands (arrows) and adrenal veins (arrowheads) in contrast-enhanced images. The thickness of right adrenal vein and left adrenal vein were measured.

Table 1. Clinical characteristics and surgical outcomes of patients with or without adrenohepatic adhesion

Characteristic	With adhesion (n=11)	Without adhesion (n=66)	p-value
Age (y)	52.8±13.9	52.4±12.1	0.91
Sex			
Male	6 (54.5)	21 (31.8)	0.18
Female	5 (45.5)	45 (68.2)	
Body mass index (kg/m^2)	23.2±3.8	23.4±3.9	0.89
History of abdominal surgery	1 (9.1)	12 (18.2)	0.68
Tumor type			
Primary aldosteronism	6 (54.5)	25 (37.9)	0.39
Pheochromocytoma	3 (27.3)	14 (21.2)	
Cushing's syndrome	1 (9.1)	21 (31.8)	
Non-functioning	1 (9.1)	6 (9.1)	
Tumor size (mm)	14.2±12.5	25.9±16.0	0.02*
Operative time (min)	177.6±33.3	186.9±56.1	0.59
Estimated blood loss (g)	13.6±23.4	20.8±62.6	0.71
Intraoperative complications			
Liver injury	5 (45.5)	2 (3.0)	<0.01*
Tumor rupture	1 (9.1)	0 (0.0)	0.35
Postoperative complications			
All	0 (0.0)	3 (4.5)	1.00
Major (grade≥III)	0 (0.0)	0 (0.0)	1.00

Values are presented as mean±standard deviation, number (%), or number only.
*p<0.05.

Table 2. Radiographic features of the patients with or without adrenohepatic adhesion

Parameter	With adhesion (n=11)	Without adhesion (n=66)	p-value
Attachment between adrenal and liver	7 (63.6)	39 (59.1)	1.00
Thickness of right/left AV (mm)			
Right vein	2.5 (2.1–4.3)	3.7 (2.8–5.0)	0.08
Left vein	3.6 (3.1–4.1)	3.5 (2.9–4.1)	0.53
Ratio of right/left AV	0.8 (0.7–0.9)	1.1 (0.9–1.3)	0.01*

Values are presented as number (%) or median (interquartile range).
AV, adrenal vein.
*p<0.05.

Table 3. Multivariate logistic regression analysis to predict adrenohepatic adhesion

Parameter	Odds ratio	95% confidence interval	p-value
Age (y)	1.01	0.94–1.08	0.77
Sex (male)	1.87	0.39–8.97	0.43
Tumor type (CS vs. other)	0.20	0.02–2.36	0.20
Tumor size (mm)	0.96	0.90–1.04	0.31
Ratio of right/left AV	0.07	0.01–0.97	0.04*

CS, Cushing's syndrome; AV, adrenal vein.
*p<0.05.

adrenal veins diameters ratio was significantly associated with AHA (Table 3).

The receiver operating characteristic curves analysis for the right/left adrenal veins ratio was performed. The sensitivity, specificity, negative predictive value and positive predictive value were 0.82, 0.76, 0.43, and 0.95 respectively when the optimal cutoff value for the ratio was 0.9 (AUC, 0.75; 95% confidence interval, 0.60–0.90).

https://doi.org/10.4111/icu.2020.61.3.277

DISCUSSION

Our study identified that small right/left adrenal veins ratio and small tumor size were possible predictive factors of AHA. Specially, AHA was found in 43% of patients with the diameter ratio <0.9. Other preoperative variables, such as age, sex or BMI are not associated with AHA. Direct radiological finding of AHA doesn't reflect actual intraoperative findings because the liver and adrenal gland appeared to be in close contact in both adhesion and non-adhesion cases.

The right/left adrenal veins diameters ratio was significantly small in those with adhesion in our study. The difference size in adrenal vein in AHA was first hypothesized by Park et al. [8]. The adrenal vein is usually single [10]. When the adrenohepatic connection exists, the hepatic vein can act as an additional pathway of venous return. In turn, the diameter of the right adrenal vein might decrease as the adrenohepatic venous circulation increases. Since the diameter of veins differs by individual, we adopted the right/left adrenal veins ratio instead of its size. Our data showed good accuracy of the right/left adrenal veins ratio to predict AHA with 82% sensitivity and 76% specificity. Herein, we couldn't measure the diameter of the bilateral adrenal veins in some patients because of low imaging quality. Thin-slice and three-dimensional CT scans, with contrast if possible, will be needed for appropriate measurements and further investigation.

The small tumor size was associated with AHA in our study. Regarding tumor type, AHA was more frequently seen in patients with PA or pheochromocytoma, whereas most of patients with CS were without AHA. These factors were not statistically significant in multivariate analysis, but small sample size might affect the results. These factors suggest that formation of AHA is not only the congenital phenomenon. Although the precise mechanism of AHA is not known, anomaly of periadrenal mesenchymal differentiation was believed to be a cause of AHA [1,11]. On the other hand, Honma [12] showed that the incidence of adrenohepatic fusion was higher in older patients, suggesting that the fusion could be an acquired event. It can be explained as follows why AHA was less common in large adrenal tumors and CS. The normal adrenal gland became atrophic as a result of compression by large adrenal tumor or decreased adrenocorticotropic hormone in CS patients. The tumors with small amount of normal adrenal gland would be easily separated from liver. Another possibility is that inflammation induced by pheochromocytoma or diagnostic procedures (e.g., adrenal vein sampling) might affect the formation of AHA. Surgeons should be mindful of the possibility of AHA especially in patients with small PA or pheochromocytoma during right adrenalectomy.

Radiologically, attachment of the liver and adrenal gland was frequently found in both the adhesion and non-adhesion groups, indicating that this imaging feature cannot distinguish AHA. Several case reports suggested that the adrenal gland abutting the liver was a sign of adrenohepatic fusion [8,13]. Our findings, however, seem to negate this idea.

In this study, 45.5% of patients with AHA experienced liver injury during laparoscopic adrenalectomy. Laparoscopic adrenalectomy is considered to be standard of care for benign adrenal tumors [14,15]. The intraoperative complication rate is less than 9%, with a range of 2.9% to 15.5% [16]. This procedure is nowadays common in training of laparoscopic surgery for urology residents [17]. Most of adrenalectomy in this study was performed by surgeon under training. The operative time in this study was longer than previous reports [18,19], but was comparable to the reports of initial experience [20]. The surgeons sometimes had difficulty with separation between the liver and adrenal gland, and that motivated us to conduct this study. Therefore, recognition and prediction of AHA is very important to avoid unnecessary complications. When surgeons encounter AHA, partial adrenalectomy and coagulation of remnant adrenal tissue should be performed for benign tumors. If complete excision is desired, combined resection of the liver capsule is necessary [7].

We use the term "adrenohepatic adhesion" instead of "adrenohepatic fusion". According to Honoré and O'Hara [1], adrenohepatic "fusion" is defined as parenchymal mixing of liver and adrenal gland, whereas adrenohepatic "adhesion" is defined that liver and adrenal gland share the capsule with no intervening fat cell. Although "adrenohepatic fusion" was mostly used in previous studies, even without histological analysis [21,22], exact diagnosis of adrenohepatic "fusion" need to confirm cellular intermingling. As we showed in Fig. 2, Adhesion alone, rather than fusion, may make it difficult to detach the liver and adrenal glands during surgery. Further investigation is necessary to examine the difference of clinical characteristics in adrenohepatic "fusion" and "adhesion".

This study has several limitations. First, it was a retrospective study with a small number of patients in whom to identify possible factors associated with AHA. A large, prospective study will be necessary to prove our hypothesis. The evidence to support our risk factor is also sparse. Basic or animal research to clarify the development of AHA should be also done. Second, histopathological analysis could not be performed because complete adrenal resection with hepatic capsules was not selected in most of the patients with adhesion. Complete resection of attached tissue is usually overtreatment for benign adrenal tumors. Third, radiographic data were useful for limited number of patients to assess AHA. The adrenal vein diameter in patients with only non-enhanced CT was difficult in most of cases. We tried to avoid interpretation bias by blinding the radiography reader, but a standard protocol for imaging should be established for further evaluation.

CONCLUSIONS

our study identified a decreased right/left adrenal veins diameters ratio as possible predictive factor of AHA. Surgeon should be alert to AHA-induced liver injury especially when the diameter ratio <0.9. Further study to confirm these findings is necessary for preoperative prediction of AHA to improve surgical quality and avoid complications.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

ACKNOWLEDGMENTS

We thank Nancy Schatken, BS, MT (ASCP), from Edanz Group (www.edanzediting.com/ac), for editing a draft of this manuscript.

AUTHORS' CONTRIBUTIONS

Research conception and design: Katsuhiro Ito. Data acquisition: Katsuhiro Ito and Hiromasa Araki. Statistical analysis: Katsuhiro Ito. Data analysis and interpretation: Katsuhiro Ito. Drafting of the manuscript: Katsuhiro Ito. Critical revision of the manuscript: Toshihiro Uchida, Yumi Manabe, Yu Miyazaki, Haruki Itoh, and Mutsuki Mishina. Administrative, technical, or material support: Hiroshi Okuno. Supervision: Hiroshi Okuno. Approval of the final manuscript: Hiroshi Okuno.

SUPPLEMENTARY MATERIAL

Scan this QR code to see the supplementary material, or visit https://www.icurology.org/src/sm/icurology-61-277-s001.pdf.

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