

WFUMB guidelines and recommendations on the clinical use of ultrasound elastography: Part3; Liver	Ferraioli G, Filice C, Castera L, Choi B, Sporea I, Wilson S, Cosgrove D, Dietrich C, Amy D, Bamber J, Barr R, Chou Y, Ding H, Farrokh A, Friedrich-Rust M, Hall T, Nakashima K, Nightingale K, Palmeri M, Schafer F, Shiina T, Suzuki S, <u>Kudo M</u>	Ultrasound Med Biol	2015 (in press)	国外
Primary leiomyosarcoma of the colon	Kono M, Tsuji N, Ozaki N, Matsumoto N, Takaba T, Okumura N, Kawasaki M, Tomita T, Umehara Y, Taniike S, Hatabe S, Funai S, Ono Y, Ochiai K, Maekura S, <u>Kudo M</u>	Clin J Gastroenterol	2015 (in press)	国外
Clinical practice guidelines for hepatocellular carcinoma differ between Japan, United States, and Europe	<u>Kudo M</u>	Liver Cancer	2015 (in press)	国外
Cold-inducible RNA-binding protein (Cirp) promotes the development of liver cancer	Sakurai T, Yada N, Watanabe T, Arizumi T, Hagiwara S, Ueshima K, Nishida N, Fujita J, <u>Kudo M</u>	Cancer Sci	2015 (in press)	国内
Safety and efficacy of tigatuzumab plus sorafenib as first-line therapy in subjects with advanced hepatocellular carcinoma: a phase 2 randomized study	Cheng AL, Kang YK, He AR, Lim HY, Ryoo BY, Hung CH, Sheen IS, Izumi N, Austin T, Wang Q, Greenberg J, Shiratori S, Beckman RA, <u>Kudo M</u> and the investigators' study group	J Hepatol	2015 (in press)	国外
Heat shock protein A4 controls cell migration and gastric ulcer healing	Sakurai T, Kashida H, Hagiwara S, Nishida N, Watanabe T, Fujita J, <u>Kudo M</u>	Digest Dis Sci	2015 (in press)	国外
Malignant transformation of hepatocellular adenoma: How frequently does it happen?	<u>Kudo M</u>	Liver Cancer	1:1-5, 2015	国外
Involvement of heat shock protein A4/Apg-2 in refractory inflammatory bowel disease	Adachi T, Sakurai T, Kashida H, Mine H, Hagiwara S, Matsui S, Yoshida K, Nishida N, Watanabe T, Itoh K, Fujita J, <u>Kudo M</u>	Inflamm Bowel Dis	21:31-39, 2015	国外
Comparison of systems for assessment of post-therapeutic response to sorafenib for hepatocellular carcinoma	Arizumi T, Ueshima K, Takeda H, Osaki Y, Takita M, Inoue T, Kitai S, Yada N, Hagiwara S, Minami Y, Sakurai T, Nishida N, <u>Kudo M</u>	J Gastroenterol	49:1578-1587, 2014	国内
NOD2 Down-regulates colonic inflammation by IRF4-mediated inhibition of K63-linked polyubiquitination of RICK and TRAF6	Watanabe T, Asano N, Meng G, Yamashita K, Arai Y, Sakurai T, <u>Kudo M</u> , Fuss IJ, Kitani A, Shimosegawa T, Chiba T, Strober W	Mucosal Immunol	7:1312-1325, 2014	国外

Stress response protein Cirp links inflammation and tumorigenesis in colitis-associated cancer	Sakurai T, Kashida H, Watanabe T, Hagiwara S, Mizushima T, Iijima H, Nishida N, Higashitsuji H, Fujita J, <u>Kudo M</u>	Cancer Res	74:6119-6128, 2014	国外
Dynamic changes of the inflammation based index (IBI) predict mortality following chemoembolization for hepatocellular carcinoma: a prospective study	Pinato DJ, Karamanakos G, Arizumi T, Adjogatse D, Kim YW, <u>Kudo M</u> , Jang JW, Sharma R	Aliment Pharm Ther	40:1270-1281, 2014	国外
Prospective Multicenter Randomized Controlled Trial of Histological Diagnostic Yield Comparing 25G EUS-FNA Needles With and Without a Core Trap in Patients With Solid Pancreatic Masses	Ashida R, Yasukawa S, Yanagisawa A, Kamata K, <u>Kudo M</u> , Ogura T, Higuchi K, Fukutake N, Nebiki H, Hirose S, Hoki N, Asada M, Yazumi S, Takaoka M, Okazaki K, Matsuda F, Okabe Y, Kitano M	Gastrointest Endosc	79:AB111, 2014	国外
Brivanib as adjuvant therapy to transarterial chemoembolization in patients with hepatocellular carcinoma: a randomized phase 3 trial	<u>Kudo M</u> , Han G, Finn RS, Poon RTP, Blanc JF, Yan L, Yang J, Lu L, Tak WY, Yu X, Lee JH, Lin SM, Wu C, Tanwandee T, Shao G, Walters IB, Cruz CD, pouart V, Wang JH	Hepatology	60:1697-1707, 2014	国外
Ultrasound elastography correlates treatment response by antiviral therapy in patients with chronic hepatitis C	Yada N, Sakurai T, Minami T, Arizumi T, Takita M, Inoue T, Hagiwara S, Ueshima K, Nishida N, <u>Kudo M</u>	Oncology	87:118-123, 2014	国外
Efficacy and safety of Telaprevir-based antiviral treatment for elderly patients with hepatitis C virus	Takita M, Hagiwara S, <u>Kudo M</u> , Kono M, Chishina H, Arizumi T, Kitai S, Yada N, Inoue T, Minami Y, Ueshima K	Oncology	87:110-117, 2014	国外
Characteristics of long-term survivors following sorafenib treatment for advanced hepatocellular carcinoma: report of a workshop at the 50th annual meeting of the Liver Cancer Study Group of Japan	Tanaka K, Shimada M, <u>Kudo M</u>	Oncology	87:104-109, 2014	国外
Treatment of hepatocellular carcinoma with Child-Pugh C cirrhosis	Nouso K, Kokudo N, Tanaka M, Kuromatsu R, Nishikawa H, Toyoda H, Oishi N, Kuwaki K, Kusanaga M, Sakaguchi T, Morise Z, Kitai S, <u>Kudo M</u>	Oncology	87:99-103, 2014	国外
Treatment strategies of Intermediate-stage hepatocellular carcinomas in Japan (Barcelona clinic liver cancer stage B)	Yamakado K, <u>Kudo M</u>	Oncology	87:78-81, 2014	国外
Recent progress in radiofrequency ablation therapy for hepatocellular carcinoma	Ikeda K, Osaki Y, Nakanishi H, Nasu A, Kawamura Y, Jyoko K, Sano T, Sunakozaka H, Uchino Y, Minami Y, Saito Y, Nagai K, Inokuchi R, Kokubu S, <u>Kudo M</u>	Oncology	87:73-77, 2014	国外

Noninvasive diagnosis of liver fibrosis: utility of data mining of both ultrasound elastography and serological findings to construct a decision tree	Yada N, <u>Kudo M</u> , Kawada N, Sato S, Osaki Y, Ishikawa A, Miyoshi H, Sakamoto M, Kage M, Nakashima O, Tonomura A	Oncology	87:63-72, 2014	国外
Combination guidance of contrast-enhanced US and fusion imaging in radiofrequency ablation for hepatocellular carcinoma with poor conspicuity on contrast-enhanced US/fusion imaging	Minami T, Minami Y, Chishina H, Arizumi T, Takita M, Kitai S, Yada N, Inoue T, Hagiwara S, Ueshima K, Nishida N, <u>Kudo M</u>	Oncology	87:55-62, 2014	国外
Virtual sonography for novice sonographer: usefulness of synapse vincent(R) with pre-check imaging of tumor location	Ogawa C, Minami Y, Morioka Y, Noda A, Arasawa S, Izuta M, Kubo A, Matsunaka T, Tamaki N, Shibatouge M, <u>Kudo M</u>	Oncology	87:50-54, 2014	国外
Pathological diagnosis of benign hepatocellular nodular lesions based on the new world health organization classification	Kondo F, Fukusato T, <u>Kudo M</u>	Oncology	87:37-49, 2014	国外
Validation of the criteria of transcatheter arterial chemoembolization failure or refractoriness in patients with advanced hepatocellular carcinoma proposed by LCSGJ	Arizumi T, Ueshima K, Chishina H, Kono M, Takita M, Kitai S, Inoue T, Yada N, Hagiwara S, Minami Y, Sakurai T, Nishida N, <u>Kudo M</u>	Oncology	87:32-36, 2014	国外
Transarterial chemoembolization failure/refractoriness: JSH-LCSGJ criteria 2014 update	<u>Kudo M</u> , Matsui O, Izumi N, Kadoya M, Okusaka T, Miyayama S, Yamakado K, Tsuchiya K, Ueshima K, Hiraoka A, Ikeda M, Ogasawara S, Yamashita T, Minami T, on behalf of the Liver Cancer Study Group of Japan	Oncology	87:22-31, 2014	国外
Surveillance and diagnostic algorithm for hepatocellular carcinoma proposed by the Liver Cancer Study Group of Japan: 2014 update	<u>Kudo M</u> , Matsui O, Izumi N, Iijima H, Kadoya M, Imai Y, on behalf of the Liver Cancer Study Group of Japan	Oncology	87:7-21, 2014	国外
Breakthroughs in the management of hepatocellular carcinoma: celebrating 50 years of the Liver Cancer Study Group of Japan	<u>Kudo M</u>	Oncology	87:1-6, 2014	国外
Accuracy of real-time tissue elastography for the evaluation of hepatic fibrosis in patients with chronic hepatitis B: a prospective multicenter study	Wu T, Ren J, Cong SZ, Meng FK, Yang H, Luo Y, Lin HJ, Sun Y, Wang XY, Pei SF, Zheng Y, He Y, Chen Y, Hu Y, Yang N, Li P, <u>Kudo M</u> , Zheng RQ	Digest Dis	32:791-799, 2014	国外
Clinical features of vascular disorders associated with chronic hepatitis virus infection	Nishida N, <u>Kudo M</u>	Digest Dis	32:786-790, 2014	国外
Identification of epigenetically inactivated genes in human hepatocellular carcinoma by integrative analyses of methylation profiling and pharmacological unmasking	Nishida N, Chishina H, Arizumi T, Takita M, Kitai S, Yada N, Hagiwara S, Inoue T, Minami Y, Ueshima K, Sakurai T, <u>Kudo M</u>	Digest Dis	32:740-746, 2014	国外

Decreased blood flow after sorafenib administration is an imaging biomarker to predict overall survival in patients with advanced hepatocellular carcinoma	Arizumi T, Ueshima K, Chishina H, Kono M, Takita M, Kitai S, Inoue T, Yada N, Hagiwara S, Minami Y, Sakurai T, Nishida N, <u>Kudo M</u>	Digest Dis	32:733-739, 2014	国外
Validation of three staging systems for hepatocellular carcinoma (JIS score, biomarker-combined JIS score, and BCLC system) in 4,649 cases from a Japanese nationwide survey	Kitai S, <u>Kudo M</u> , Izumi N, Kaneko S, Ku Y, Kokudo N, Sakamoto M, Takayama T, Nakashima O, Kadoya M, Matsuyama Y, Matsunaga T, for the Liver Cancer Study Group of Japan	Digest Dis	32:717-724, 2014	国外
Duration of stable disease is associated with overall survival in patients with advanced hepatocellular carcinoma treated with sorafenib	Arizumi T, Ueshima K, Chishina H, Kono M, Takita M, Kitai S, Inoue T, Yada N, Hagiwara S, Minami Y, Sakurai T, Nishida N, <u>Kudo M</u>	Digest Dis	32:705-710, 2014	国外
Ultrasound fusion imaging of hepatocellular carcinoma: a review of current evidence	Minami Y, <u>Kudo M</u>	Digest Dis	32:690-695, 2014	国外
Radiofrequency ablation for hepatocellular carcinoma measuring 2 cm or smaller: Results and risk factors for local recurrence	Kono M, Inoue T, <u>Kudo M</u> , Chishina H, Arizumi T, Takita M, Kitai S, Yada N, Hagiwara S, Minami Y, Ueshima K, Nishida N, Murakami T	Digest Dis	32:670-677, 2014	国外
Genome-wide profiling of DNA methylation and tumor progression in human hepatocellular carcinoma	Nishida N, Nishimura T, Nakai T, Chishina H, Arizumi T, Takita M, Kitai S, Yada N, Hagiwara S, Inoue T, Minami Y, Ueshima K, Sakurai T, <u>Kudo M</u>	Digest Dis	32:658-663, 2014	国外
Emerging strategies for the management of hepatocellular carcinoma	<u>Kudo M</u>	Digest Dis	32:655-657, 2014	国外
JSH consensus-based clinical practice guidelines for the management of hepatocellular carcinoma: 2014 update by the Liver Cancer Study Group of Japan	<u>Kudo M</u> , Matsui O, Izumi N, Iijima H, Kadoya M, Imai Y, Okusaka T, Miyayama S, Tsuchiya K, Ueshima K, Hiraoka A, Ikeda M, Ogasawara S, Yamashita T, Minami T, Yamakado K, on behalf of the Liver Cancer Study Group of Japan	Liver Cancer	3:458-468, 2014	国外
Alteration of epigenetic profile in human hepatocellular carcinoma and its clinical implications	Nishida N, <u>Kudo M</u>	Liver Cancer	3:417-427, 2014	国外
Biomarkers and personalized sorafenib therapy	<u>Kudo M</u>	Liver Cancer	3:399-404, 2014	国外
Current treatment status of polycystic liver disease in Japan	Ogawa K, Fukunaga K, Takeuchi T, Kawagishi N, Ubara Y, <u>Kudo M</u> , Ohkohchi N	Hepatol Res	44:1110-1118, 2014	国内

Prognostic impact of spontaneous tumor rupture in patients with hepatocellular carcinoma: an analysis of 1,160 cases from a nationwide survey	Aoki T, Kokudo N, Matsuyama Y, Izumi N, Ichida T, <u>Kudo M</u> , Ku Y, Sakamoto M, Nakashima O, Matsui O, Makuuchi M, for the Liver Cancer Study Group of Japan	Ann Surg	259:532-542, 2014	国外
Serum amyloid A and C-reactive protein positive nodule in alcoholic liver cirrhosis, hard to make definite diagnosis	Kim SR, Kondo F, Otono Y, Imoto S, Ando K, Hirakawa M, Fukuda K, Sakaki M, Kim SK, Komaki T, Tsuchida S, Kobayashi S, Matsuoka T, <u>Kudo M</u>	Hepatol Res	44:584-590, 2014	国内
Nationwide survey in Japan regarding splenectomy/partial splenic embolization for interferon treatment targeting hepatitis C virus-related chronic liver disease in patients with low platelet count	Ikeda N, Imanishi H, Aizawa N, Tanaka H, Iwata Y, Enomoto H, Siato M, Iijima H, Iimuro Y, Fujimoto J, Yamamoto S, Hirota S, <u>Kudo M</u> , Arii S, Nishiguchi S	Hepato Res	44:829-836, 2014	国外
Effect of everolimus on survival in advanced hepatocellular carcinoma after failure of sorafenib: The EVOLVE-1 randomized clinical trial	Zhu AX, <u>Kudo M</u> , Assenat E, Cattani S, Kang YK, Lim HY, Poon RTP, Blanc JF, Vogel A, Chen CL, Dorval E, Radosavljevic MPR, Santoro A, Daniele B, Furuse J, Jappe A, Perraud K, Anak O, Sellami DB, Chen LT	J Am Med Assoc (JAMA)	312:57-67, 2014	国外
Homozygous deletion of the activin A receptor, type 1B gene is associated with an aggressive cancer phenotype in pancreatic cancer	Togashi Y, Sakamoto H, Hayashi H, Terashima M, Velasco Ma, Fujita Y, Kodera Y, Sakai K, Tomida S, Kitano M, <u>Kudo M</u> , Nishio K	Mol Cancer	13:126-136, 2014	国外
Recent advances in Bioinformatics reveal the molecular heterogeneity of hepatocellular carcinoma	<u>Kudo M</u>	Liver Cancer	3:68-70, 2014	国外
ART score for repeated transarterial chemoembolization in patients with hepatocellular carcinoma	<u>Kudo M</u> , Arizumi T, Ueshima K	Hepatology	59:2424-2425, 2014	国外
GIDEON (Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and Of its treatment with sorafenib): second interim analysis	Lencioni R, <u>Kudo M</u> , Ye SL, Bronowicki JP, Chen XP, Dagher L, Furuse J, Geschwind JF, de Guevara LL, Papandreou C, Takayama T, Yoon SK, Nakajima K, Lehr R, Heldner S, Sanyal AJ	Int J Clin Pract	68:609-617, 2014	国外
The gross classification of hepatocellular carcinoma: usefulness of contrast-enhanced US	Hatanaka K, Minami Y, <u>Kudo M</u> , Inoue T, Chung H, Haji S	J Clin Ultrasound	42:1-8, 2014	国外
Relevance of the core 70 and IL-28B polymorphism and response-guided therapy of peginterferon alfa-2a± ribavirin for chronic hepatitis C of genotype 1b: A multicenter randomized trial, ReGIT-J study	Nishiguchi S, Enomoto H, Aizawa N, Nishikawa H, Osaki Y, Tsuda Y, Higuchi K, Okazaki K, Seki T, Kim SR, Hongo Y, Jyomura H, Nishida N, <u>Kudo M</u>	J Gastroenterol	49:492-501, 2014	国内

Therapeutic Response Assessment of RFA for HCC: Contrast-enhanced US, CT and MRI	Minami Y, Nishida N, <u>Kudo M</u>	World J Gastroenterol	20:4160-4166, 2014	国外
Tracking Navigation Imaging of Transcatheter Arterial Chemoembolization for Hepatocellular Carcinoma using Three-Dimensional Cone-Beam CT Angiography	Minami Y, Yagyu Y, Murakami T, Kudo M	Liver Cancer	3:53-61, 2014	国外
Quantitative levels of hepatitis B virus DNA and surface antigen and the risk of hepatocellular carcinoma in patients with hepatitis B receiving long-term nucleos(t)ide analogue therapy	Kawanaka M, Nishio K, Nakamura J, Oka T, Urata N, Goto D, Suehiro M, Kawamoto H, <u>Kudo M</u> , Yamada G	Liver Cancer	3:41-52, 2014	国外
Prediction of incidence risk of hepatocellular carcinoma by ultrasound elastography	<u>Kudo M</u>	Liver Cancer	3:1-5, 2014	国外
Re-evaluating transarterial chemoembolization for the treatment of hepatocellular carcinoma: consensus recommendations and review by an international expert panel	Cheng AL, Amarapurkar D, Chao Y, Chen PJ, Geschwind JF, Goh KL, Han KH, <u>Kudo M</u> , Lee HC, Lee RC, Lesmana LA, Lim HY, Paik SW, Poon RT, Tan CK, Tanwandee T, Teng G, Park JW	Liver Int	34:174-183, 2014	国外
Nationwide study of 4741 patients with non-B non-C hepatocellular carcinoma with special reference to the therapeutic impact	Utsunomiya T, Shimada M, <u>Kudo M</u> , Ichida T, Matsui O, Izumi N, Matsuyama Y, Sakamoto M, Nakashima O, Ku Y, Kokudo N, Makuuchi M for the Liver Cancer Study Group of Japan	Ann Surg	259:336-345, 2014	国外
Impact of histologically confirmed lymph node metastases on the patient survival after surgical resection for hepatocellular carcinoma: report of a Japanese nationwide survey	Hasegawa K, Makuuchi M, Kokudo N, Izumi N, Ichida T, <u>Kudo M</u> , Ku Y, Sakamoto M, Nakashima M, Matsui O, Matsuyama Y, for the Liver Cancer Study Group of Japan	Ann Surg	259:166-170, 2014	国外
Evaluation of early response to hepatic arterial infusion chemotherapy in patients with advanced hepatocellular carcinoma using the combination of RECIST and tumor markers.	Miyaki D, Kawaoka T, <u>Aikata H</u> , Kan H, Fujino H, Fukuhara T, Kobayashi T, Naeshiro N, Honda Y, Tsuge M, Hiramatsu A, Imamura M, Hyogo H, Kawakami Y, Yoshimatsu R, Yamagami T, Awai K, Chayama K.	J Gastroenterol Hepatol.	2014 Oct 14. doi: 10.1111/jgh.12821.	国外
Role of 3-D conformal radiotherapy for major portal vein tumor thrombosis combined with hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma.	Fujino H, Kimura T, <u>Aikata H</u> , Miyaki D, Kawaoka T, Kan H, Fukuhara T, Kobayashi T, Naeshiro N, Honda Y, Tsuge M, Hiramatsu A, Imamura M, Kawakami Y, Hyogo H, Takahashi S, Yoshimatsu R, Yamagami T, Kenjo M, Nagata Y, Awai K, Chayama K.	Hepatol Res.	2014 Jul 23. doi: 10.1111/hepr.12392.	国内

Pilot study of stereotactic body radiation therapy combined with transcatheter arterial chemoembolization for small hepatocellular carcinoma.	Honda Y, Kimura T, <u>Aikata H</u> , Nakahara T, Naeshiro N, Tanaka M, Miyaki D, Nagaoki Y, Kawaoka T, Takaki S, Hiramatsu A, Waki K, Ishikawa M, Kakizawa H, Kenjo M, Awai K, Nagata Y, Chayama K.	Hepatogastroenterology.	2014 Jan-Feb;61(129):31-6.	国外
Clinical outcome and prognostic factors of patients with hepatocellular carcinoma and extrahepatic metastasis treated with sorafenib.	Kawaoka T, <u>Aikata H</u> , Kan H, Fujino H, Fukuhara T, Kobayashi T, Naeshiro N, Miyaki D, Hiramatsu A, Imamura M, Kawakami Y, Hyogo H, Chayama K.	Hepatol Res.	2014 Dec;44(13):1320-8.	国内
Fatty liver creates a pro-metastatic microenvironment for hepatocellular carcinoma through activation of hepatic stellate cells	Mikuriya, Y. Tashiro, H. Kuroda, S. Nambu, J. Kobayashi, T. Amano, H. Tanaka, Y. <u>Ohdan, H.</u>	Int J Cancer.	2015 Feb 15;136(4):E3-13.	国外
Rho-kinase inhibitor targeting the liver prevents ischemia/reperfusion injury in the steatotic liver without major systemic adversity in rats	Kuroda, S. Tashiro, H. Kimura, Y. Hirata, K. Tsutada, M. Mikuriya, Y. Kobayashi, T. Amano, H. Tanaka, Y. <u>Ohdan, H.</u>	Liver Transpl.	2015 Jan;21(1):123-31.	国外
Quantitative effect of natural killer-cell licensing on hepatocellular carcinoma recurrence after curative hepatectomy	Tanimine, N. Tanaka, Y. Kobayashi, T. Tashiro, H. Miki, D. Imamura, M. Aikata, H. Tanaka, J. Chayama, K. <u>Ohdan, H.</u>	Cancer Immunol Res.	2014 Dec;2(12):1142-7.	国外
Daclatasvir combined with peginterferon alfa-2a and ribavirin in Japanese patients infected with hepatitis C genotype 1	<u>Izumi N.</u> Yokosuka O, Kawada N, Osaki Y, Yamamoto K, Sata M, Ishikawa H, Ueki T, Hu W, McPhee F, A Hughes E, Kumada H.	Antivir Ther	19:501-10, 2014	国外
Clinical significance of therapy using branched-chain amino acid granules in patients with liver cirrhosis and hepatocellular carcinoma.	Nishikawa H, <u>Osaki Y.</u>	Hepatol Res	44:149-158, 2014	国内
Relevance of the Core 70 and IL-28B polymorphism and response-guided therapy of peginterferon alfa-2a ± ribavirin for chronic hepatitis C of Genotype 1b: a multicenter randomized trial, ReGIT-J study.	Nishiguchi S, Enomoto H, Aizawa N, Nishikawa H, <u>Osaki Y.</u> Tsuda Y, Higuchi K, Okazaki K, Seki T, Kim SR, Hongo Y, Jyomura H, Nishida N, Kudo M.	J Gastroenterol	49:492-501, 2014	国内

Clinical efficacy of non-transplant therapies in patients with hepatocellular carcinoma with Child-Pugh C liver cirrhosis.	Nishikawa H, Kita R, Kimura T, Ohara Y, Takeda H, Sakamoto A, Saito S, Nishijima N, Nasu A, Komekado H, <u>Osaki Y.</u>	Anticancer Res	34:3039-3044, 2014	国外
Clinical significance of the FIB-4 index for non-B non-C hepatocellular carcinoma treated with surgical resection.	Nishikawa H, <u>Osaki Y.</u> , Komekado H, Sakamoto A, Saito S, Nishijima N, Nasu A, <u>Arimoto A.</u> , Kita R, Kimura T.	Oncol Rep	33:88-94, 2015	国外
Clinical implication of the preoperative GSA index in 99mTc-GSA scintigraphy in hepatitis C virus-related hepatocellular carcinoma.	Nishikawa H, <u>Osaki Y.</u> , Komekado H, Sakamoto A, Saito S, Nishijima N, Nasu A, <u>Arimoto A.</u> , Kita R, Kimura T.	Oncol Rep	33:1071-1078, 2015	国外
Accuracy of spleen stiffness measurement in detection of esophageal varices in patients with chronic liver disease: systematic review and meta-analysis.	Singh S, Eaton JE, Murad MH, Tanaka H, <u>Iijima H.</u> , Talwalkar JA.	Clin Gastroenterol Hepatol.	12:935-45, 2014	国外
Changes in plasma vascular endothelial growth factor at 8 weeks after sorafenib administration as predictors of survival for advanced hepatocellular carcinoma.	Tsuchiya K, Asahina Y, Matsuda S, Muraoka M, Nakata T, Suzuki Y, Tamaki N, Yasui Y, Suzuki S, Hosokawa T, Nishimura T, Ueda K, Kuzuya T, Nakanishi H, Itakura J, Takahashi Y, Kurosaki M, Enomoto N, <u>Izumi N.</u>	Cancer	120:229-37, 2014	国外
Discriminal of fibrotic staging of chronic hepatitis C using multiple fibrotic markers.	Ikeda K, <u>Izumi N.</u> , Tanaka E, Yotsuyanagi H, Takahashi Y, Fukushima J, Kondo F, Fukusato T, Koike K, Hayashi N, Tsubouchi H, Kumada H.	Hepatol Res	44:1047-55, 2014	国内
Genetic variation near interleukin 28B and the risk of hepatocellular carcinoma in patients with chronic hepatitis C.	Asahina Y, Tsuchiya K, Nishimura T, Muraoka M, Suzuki Y, Tamaki N, Yasui Y, Hosokawa T, Ueda K, Nakanishi H, Itakura J, Takahashi Y, Kurosaki M, Enomoto N, Nakagawa M, Kakinuma S, Watanabe M, <u>Izumi N.</u>	J Gastroenterol	49:1152-62, 2014	国内
Prospective comparison of real-time tissue elastography and serum fibrosis markers for the estimation of liver fibrosis in chronic hepatitis C patients.	Tamaki N, Kurosaki M, Matsuda S, Nakata T, Muraoka M, Suzuki Y, Yasui Y, Suzuki S, Hosokawa T, Nishimura T, Ueda K, Tsuchiya K, Nakanishi H, Itakura J, Takahashi Y, Matsunaga K, Taki K, Asahina Y, <u>Izumi N.</u>	Hepatol Res	44:720-7, 2014	国内

Impaired brain activity in cirrhotic patients with minimal hepatic encephalopathy: Evaluation by near-infrared spectroscopy.	Nakanishi H, Kurosaki M, Nakanishi K, Tsuchiya K, Noda T, Tamaki N, Yasui Y, Hosokawa T, Ueda K, Itakura J, Anami K, Asahina Y, Enomoto N, Higuchi T, <u>Izumi N.</u>	Hepatol Res	44:319-26, 2014	国内
Efficacy of daclatasvir in hepatitis C virus	<u>Izumi N.</u>	Expert Rev Anti Infect Ther	12:1025-31, 2014	国外
Reduced organic anion transporter expression is a risk factor for hepatocellular carcinoma in chronic hepatitis C patients: a propensity score matching study	Yasui Y, Kudo A, Kurosaki M, Matsuda S, Muraoka M, Tamaki N, Suzuki S, Hosokawa T, Ueda K, Matsunaga K, Nakanishi H, Tsuchiya K, Itakura J, Takahashi Y, Tanaka S, Asahina Y, Enomoto N, Arii S, <u>Izumi N</u>	Oncology	86:53-62, 2014	国外
Virtual Sonography for Novice Sonographers: Usefulness of SYNAPSE VINCENT® with Pre-Check Imaging of Tumor Location	<u>Chikara Ogawa</u> Yasunori Minam Yumiko Morioka Akiyo Noda Soichi Arasawa Masako Izuta Atsushi Kubo Toshihiro Matsunaka Noriyuki Tamaki Mitsushige Shibatouge Masatoshi Kudo	Oncology 2014;87(suppl 1):50-54 DOI:10.1159/000368145	Published online: November 22, 2014	国外
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IV. 研究成果の刊行物・別刷

Noninvasive Diagnosis of Liver Fibrosis: Utility of Data Mining of Both Ultrasound Elastography and Serological Findings to Construct a Decision Tree

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Key Words

Data mining · Liver fibrosis · Liver fibrosis index · Real-time tissue elastography · Strain elastography

Abstract

Objective: Although liver biopsy is the gold standard for viral liver disease management, it is invasive and the sampling error rate is problematic. Real-time tissue elastography (RTE), a recently developed method of ultrasound elastography, can be used to assess liver fibrosis noninvasively but the overlap between fibrosis stages limits its ability to assess liver fibrosis adequately when used alone. **Methods:** A multi-center collaborative study involving 542 patients with chronic viral hepatitis and cirrhosis who were scheduled to undergo liver biopsy compared the image features obtained from RTE image analysis, the liver fibrosis index (LFI), and pathological diagnosis. RTE and a blood test were performed

on the same day as the liver biopsy. Data mining was also performed to construct a decision tree, and its diagnostic performance for assessing liver fibrosis was evaluated. **Results:** The LFI was higher in patients with chronic hepatitis C (CHC) than in those with chronic hepatitis B (CHB). When a decision tree was constructed by data mining of RTE and serological findings, the diagnostic accuracy was very high for all fibrosis stages, with respective rates at F1, F2, F3, and F4 of 94.4, 54.1, 38.7, and 81.3% for patients with CHC and of 97.1, 50.0, 43.8, and 80.6% for patients with CHB. **Conclusions:** The variation in LFI values between the different etiologies appears to reflect the difference in the development style of liver fibrosis. The decision tree for assessing liver fibrosis constructed by data mining of both RTE and serological findings had a high diagnostic performance in assessing liver fibrosis and shows promising clinical utility.

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Introduction

Spontaneous clearance of hepatitis C virus (HCV) almost never occurs once the infection has become chronic, so liver fibrosis progresses year after year and ultimately leads to cirrhosis in individuals with chronic hepatitis C (CHC) if they do not undergo antiviral therapy with agents such as interferons [1]. Viral hepatitis is a cause of hepatocarcinogenesis, and the incidence of liver cancer significantly increases as liver fibrosis progresses in CHC [2]. It is expected that the surveillance of liver cancer will improve detection rates of early-stage liver cancer and consequently improve prognosis through treatment, including local therapy, hepatectomy, and liver transplantation [3–9]. Liver fibrosis affects both the virus eradication rate and prognosis. Assessing liver fibrosis is therefore useful for determining the indication of treatment for viral hepatitis and predicting the risk of hepatocarcinogenesis, making it very important in clinical practice.

Liver biopsy is regarded as the gold standard for assessing liver fibrosis; however, it is an invasive technique that carries risks of bleeding and pain. Moreover, the biopsy sample evaluated is small, representing only 1/50,000 of the liver, so differences in assessment findings can arise depending on the site biopsied or the examining pathologist's judgment. One study that compared the pathological findings of liver biopsy with those of hepatectomy found a variation rate of approximately 30% [10].

Another useful assessment technique is ultrasound elastography, which noninvasively measures liver stiffness. Although liver stiffness is influenced by factors such as liver fibrosis and inflammation, it is correlated with the incidence of viral hepatocarcinogenesis, and studies have shown that the FibroScan is useful for the surveillance of liver cancer [5, 11–13]. Real-time tissue elastography (RTE), an ultrasound elastography with another measurement principle, noninvasively depicts the distortion in liver tissue caused by beating of the heart in real time; as liver fibrosis progresses, the percentage of blue low-strain areas and the textural disorganization increase [14, 15]. A verification study using a mechanical model of liver fibrosis suggested that changes in RTE images associated with the progression of liver fibrosis are seen because RTE is actually depicting liver fibrosis itself [16]. In addition, the liver fibrosis index (LFI), which is a multiple regression equation for assessing liver fibrosis using liver fibrosis estimates based on biopsy and RTE data obtained from patients with CHC and cirrhosis, is widely used as a technique for assessing

liver fibrosis with RTE as it can be easily measured with RTE systems [17–20]. However, the LFI was developed based on data from patients with CHC and cirrhosis, and its usefulness for other etiologies has not been sufficiently discussed. Furthermore, the stage of fibrosis is often not completely clear when using the LFI in clinical practice, due to the large amount of overlap between the stages, so an assessment method with greater diagnostic accuracy is needed.

Against this background, in this study we examined differences between patients with CHC and chronic hepatitis B (CHB) by comparing image features from RTE image analysis, the LFI, and serological tests. We also constructed a decision tree by data mining both RTE and serological findings and evaluated its diagnostic performance for assessing liver fibrosis.

Patients and Methods

Patients

This was a multicenter collaborative study conducted at Kinki University Hospital, Osaka City University Hospital, Shimane University Hospital, Osaka Red Cross Hospital, Hitachi General Hospital, Kagawa University Hospital, Minami Wakayama Medical Center, Kumamoto Shinto General Hospital, Nagoya City University Hospital, Wakayama Medical University Hospital, Osaka Medical Center for Cancer and Cardiovascular Diseases, Ehime University Hospital, Takamatsu Red Cross Hospital, Tottori University Hospital, Yashiro General Hospital, Hyogo College of Medicine Hospital, and PL Hospital. Only patients chronically infected with either HCV or hepatitis B virus (HBV) were included (coinfected patients were excluded). The strain of hepatitis virus was determined based on whether a positive result was obtained when HCV-RNA and HBV-DNA were measured. Furthermore, patients who consumed ≥ 20 g of alcohol per day or had another type of chronic hepatitis such as primary biliary cirrhosis or autoimmune hepatitis were excluded. The study protocol conformed to the Declaration of Helsinki and was approved by the ethics committee of each participating institute. Informed consent to participate in the study was obtained from each patient.

Clinical and Laboratory Assessments

A blood test and RTE were performed on the same day as the liver biopsy. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), total bilirubin (T-Bil), platelet count (PLT), prothrombin time (PT), international normalized ratio (INR), hyaluronic acid (HA), type IV collagen, type IV collagen 7S domain, type III procollagen N-peptide (P3P), and matrix metalloproteinase-3 (MMP3) were assessed using automated methods.

Histological Assessment

Percutaneous ultrasound-guided liver biopsy was performed on the right lobe with a Tru-Cut semiautomatic 16- or 18-gauge needle apparatus. The liver biopsy specimens were fixed in for-

malin, embedded in paraffin, and stained with hematoxylin and eosin, Masson's trichrome or Azan. All biopsy specimens were examined by 3 liver pathology experts who were blinded to the patient characteristics. Liver fibrosis was scored by the new Inuyama classification, the Japanese criteria for the histological assessment of chronic viral hepatitis [21]. The 3 pathologists assessed each case separately and differences in judgments were resolved by consensus. The stage of fibrosis was classified as follows: F0 = no fibrosis; F1 = fibrosis portal expansion; F2 = bridging fibrosis (portal-portal or portal-central linkage); F3 = bridging fibrosis with lobular distortion (disorganization), or F4 = cirrhosis.

Real-Time Tissue Elastography

The principle of RTE has been already reported by us [14, 15, 18–20, 22, 23]. Briefly, RTE was performed using ultrasonography (EUS-8500, HI-VISION 900, and HI-VISION Ascendus; Hitachi Aloka Medical, Tokyo, Japan) and the EUP-L52 linear probe (3–7 MHz; Hitachi Aloka Medical). Patients were examined in the spine position with the right arm in maximal abduction and were instructed to hold their breath. The examinations were performed on the right lobe through the intercostal spaces, with the transducer held firmly with no compression applied to the skin. The B-mode and static image superimposed on B-mode were both visualized in real time, enabling the optimal position to be easily selected. The region of interest of the strain image was 2.5 cm² and located about 1 cm below the surface of the liver. In addition, to obtain good images, scanning was performed to avoid large vessels and attenuation by the lungs and ribs. Videos comprising stable RTE images over ≥ 5 sequential heartbeats were saved 3 times. A reader blinded to patient characteristics selected 10 appropriate images from the saved videos using the electrocardiogram and strain graph as references and analyzed those images. As RTE is a technique for depicting relative strain, artifacts within the region of interest affect the results and therefore the reader selected images with few artifacts and then analyzed the areas without artifacts in these images. From each RTE image, 11 image features were extracted: mean relative strain value (MEAN); standard deviation of relative strain value (SD); percentage of low strain area (percentage of the blue colored area; %AREA); complexity of low strain area (calculated as square of perimeter divided by area; COM); skewness (SKEW); kurtosis (KURT); contrast (CON); entropy (ENT); textural complexity, inverse difference moment (IDM); angular second moment (ASM), and correlation (COR). LFI was calculated using a previously reported method [17–19].

Statistical Analysis

Descriptive statistics are shown as median and quartile, or percentage as appropriate. Differences in findings by etiology were evaluated using the nonparametric Mann-Whitney U test. Differences in findings by fibrosis stage were evaluated by multiple comparisons with Tukey's honestly significant difference test and trend analysis with the Jonckheere-Terpstra trend test. Differences were considered statistically significant at $p < 0.05$. The diagnostic performance for liver fibrosis was determined in terms of sensitivity, specificity, positive predictive value, negative predictive value, diagnostic accuracy, and area under the receiver operating characteristic curve (AUROC). All analyses were performed using SPSS Statistics 20 (IBM, Armonk, N.Y., USA).

Results

Demographics and Baseline Features

A total of 542 patients with good RTE images, good samples from liver biopsy, and with liver fibrosis were included in the analysis. The pathological diagnosis was HCV in 414 patients (F1: 179, F2: 98, F3: 62, and F4: 75) and HBV in 128 patients (F1: 69, F2: 12, F3: 16, and F4: 31).

Comparison of Serological Markers and Pathological Diagnosis

In the HCV-infected patients, as the stage of fibrosis progressed, a significant increasing trend was seen for AST, ALT, GGT, T-Bil, INR, HA, type IV collagen, type IV collagen 7S, and P3P ($p < 0.0001$), a significant decreasing trend was seen for PLT ($p < 0.0001$), and no significant trend was seen for MMP3 ($p = 0.565$). In the HBV-infected patients, as the stage of fibrosis progressed, a significant increasing trend was seen for GGT, INR, HA, type IV collagen, and type IV collagen 7S ($p < 0.0001$), a significant decreasing trend was seen for PLT ($p < 0.0001$), and no significant trend was seen for AST, ALT, T-Bil, P3P, and MMP3 ($p = 0.565$) (tables 1, 2).

Relationship between Liver Fibrosis Stage, RTE Image Features and LFI

As the stage of fibrosis progressed in the HCV-infected patients, a significant decreasing trend was seen for MEAN ($p < 0.0001$), a significant increasing trend was seen for SD, AREA, COM, CON, and SKEW ($p < 0.0001$), and no significant trend was seen for ASM, COR, ENT, IDM, and KURT. As the stage of fibrosis progressed in the HBV-infected patients, a significant decreasing trend was seen for MEAN ($p < 0.0001$), a significant increasing trend was seen for SD, AREA, COM, CON, and SKEW ($p < 0.0001$) as well as for KURT ($p = 0.001$), and no significant trend was seen for ASM, COR, ENT, and IDM.

A significant increasing trend was seen for the LFI in both HCV- and HBV-infected patients ($p < 0.0001$). Multiple comparisons between stages of fibrosis revealed a significant difference in the LFI between all stages of fibrosis in HCV-infected patients (F1 vs. F2, F1 vs. F3, F1 vs. F4, F2 vs. F3, F2 vs. F4, and F3 vs. F4). In HBV-infected patients, however, the only significant differences were between F1/F4 and F2/F4 (table 3).

Comparison of the LFI between HCV and HBV

When the LFI was compared between HCV- and HBV-infected patients at each stage of fibrosis, it was

Table 1. Comparison of serological markers and pathological fibrosis diagnosis

	HCV				p value	HBV				p value
	F1 (n = 179)	F2 (n = 98)	F3 (n = 62)	F4 (n = 75)		F1 (n = 69)	F2 (n = 12)	F3 (n = 16)	F4 (n = 31)	
<i>Serum markers</i>										
AST, IU/ml	33.0 (24.0, 51.0)	46.0 (30.0, 71.0)	66.5 (45.3, 111.0)	59.0 (44.0, 89.0)	<0.0001	33.0 (23.0, 58.5)	51.0 (21.0, 138.0)	43.5 (26.3, 80.0)	36.0 (25.3, 45.8)	0.619
ALT, IU/ml	38.0 (24.0, 56.0)	51.0 (29.0, 92.0)	66.5 (45.3, 117.0)	52.0 (32.0, 94.0)	<0.0001	34.0 (19.0, 110.0)	93.0 (23.0, 165.0)	58.5 (22.0, 74.3)	31.5 (17.8, 46.8)	0.315
GGT, IU/ml	29.0 (19.0, 57.0)	37.0 (22.0, 65.0)	43.5 (29.0, 69.5)	43.0 (25.0, 62.0)	<0.0001	26.0 (16.0, 46.5)	35.0 (18.0, 40.0)	57.0 (36.0, 89.8)	42.5 (26.5, 120.0)	<0.0001
T-Bil, mg/dl	0.70 (0.05, 0.90)	0.70 (0.50, 0.90)	0.75 (0.60, 1.08)	0.90 (0.70, 1.45)	<0.0001	0.60 (0.50, 0.85)	0.70 (0.60, 0.80)	0.70 (0.53, 0.98)	0.90 (0.60, 1.70)	0.005
PLT	19.4 (15.3, 22.2)	16.5 (12.3, 19.7)	12.8 (9.53, 16.2)	9.2 (6.6, 12.7)	<0.0001	20.4 (16.5, 26.9)	18.0 (15.1, 19.8)	15.6 (14.3, 19.8)	10.7 (7.8, 15.1)	<0.0001
INR	0.98 (0.94, 1.02)	1.02 (0.96, 1.06)	1.07 (1.01, 1.11)	1.14 (1.08, 1.23)	<0.0001	1.02 (0.99, 1.06)	1.06 (0.98, 1.10)	1.05 (0.99, 1.13)	1.10 (1.02, 1.14)	<0.0001
HA, ng/ml	38.0 (25.2, 75.8)	71.0 (41.0, 115.0)	233.2 (89.0, 413.0)	314.1 (170.8, 513.3)	<0.0001	26.8 (19.3, 45.1)	39.0 (25.0, 90.0)	87.1 (34.8, 148.0)	109.5 (83.2, 193.3)	<0.0001
Collagen type, ng/ml										
IV	116.0 (93.5, 145.5)	126.0 (96.5, 158.0)	181.0 (141.3, 232.0)	246.0 (174.0, 312.0)	<0.0001	104.0 (90.0, 125.5)	124.0 (79.3, 155.8)	153.5 (100.3, 224.8)	171.0 (119.0, 193.0)	<0.0001
IV 7S	4.4 (3.7, 5.2)	5.3 (4.4, 6.1)	7.2 (5.7, 8.9)	8.6 (7.0, 11.0)	<0.0001	4.0 (3.5, 4.9)	4.4 (3.8, 5.4)	5.7 (4.2, 6.7)	5.8 (5.0, 7.1)	<0.0001
P3P, U/ml	0.79 (0.66, 0.90)	0.80 (0.71, 1.00)	1.05 (0.83, 1.30)	1.10 (0.90, 1.30)	<0.0001	0.58 (0.50, 0.70)	0.84 (0.65, 0.94)	0.63 (0.48, 0.81)	0.63 (0.51, 0.77)	0.201
MMP3, ng/ml	37.7 (25.6, 58.1)	34.3 (27.0, 50.4)	40.2 (24.6, 52.7)	39.0 (32.5, 55.9)	0.565	36.7 (21.2, 46.0)	51.3 (28.0, 64.1)	62.9 (37.7, 80.7)	41.1 (28.5, 51.1)	0.152

Values are presented as median (first quartile, third quartile). The p values were calculated with the Jonckheere-Terpstra trend test.

Table 2. Comparison of serological markers and etiology

	F1		p value	F2		p value	F3		p value	F4		p value
	HCV (n = 179)	HBV (n = 69)		HCV (n = 98)	HBV (n = 12)		HCV (n = 62)	HBV (n = 16)		HCV (n = 75)	HBV (n = 31)	
<i>Serum markers</i>												
AST, IU/ml	33.0 (24.0, 51.0)	33.0 (23.0, 58.5)	0.941	46.0 (30.0, 71.0)	51.0 (21.0, 138.0)	0.767	66.5 (45.3, 111.0)	43.5 (26.3, 80.0)	0.049	59.0 (44.0, 89.0)	36.0 (25.3, 45.8)	0.000
ALT, IU/ml	38.0 (24.0, 56.0)	34.0 (19.0, 110.0)	0.776	51.0 (29.0, 92.0)	93.0 (23.0, 165.0)	0.497	66.5 (45.3, 117.0)	58.5 (22.0, 74.3)	0.202	52.0 (32.0, 94.0)	31.5 (17.8, 46.8)	0.000
GGT, IU/ml	29.0 (19.0, 57.0)	26.0 (16.0, 46.5)	0.110	37.0 (22.0, 65.0)	35.0 (18.0, 40.0)	0.431	43.5 (29.0, 69.5)	57.0 (36.0, 89.8)	0.263	43.0 (25.0, 62.0)	42.5 (26.5, 120.0)	0.394
T-Bil, mg/dl	0.70 (0.05, 0.90)	0.60 (0.50, 0.85)	0.694	0.70 (0.50, 0.90)	0.70 (0.60, 0.80)	0.991	0.75 (0.60, 1.08)	0.70 (0.53, 0.98)	0.891	0.90 (0.70, 1.45)	0.90 (0.60, 1.70)	0.832
PLT	19.4 (15.3, 22.2)	20.4 (16.5, 26.9)	0.030	16.5 (12.3, 19.7)	18.0 (15.1, 19.8)	0.380	12.8 (9.53, 16.2)	15.6 (14.3, 19.8)	0.056	9.2 (6.6, 12.7)	10.7 (7.8, 15.1)	0.078
INR	0.98 (0.94, 1.02)	1.02 (0.99, 1.06)	0.000	1.02 (0.96, 1.06)	1.06 (0.98, 1.10)	0.108	1.07 (1.01, 1.11)	1.05 (0.99, 1.13)	0.741	1.14 (1.08, 1.23)	1.10 (1.02, 1.14)	0.018
HA, ng/ml	38.0 (25.2, 75.8)	26.8 (19.3, 45.1)	0.002	71.0 (41.0, 115.0)	39.0 (25.0, 90.0)	0.091	233.2 (89.0, 413.0)	87.1 (34.8, 148.0)	0.016	314.1 (170.8, 513.3)	109.5 (83.2, 193.3)	0.000
Collagen type, ng/ml												
IV	116.0 (93.5, 145.5)	104.0 (90.0, 125.5)	0.136	126.0 (96.5, 158.0)	124.0 (79.3, 155.8)	0.879	181.0 (141.3, 232.0)	153.5 (100.3, 224.8)	0.331	246.0 (174.0, 312.0)	171.0 (119.0, 193.0)	0.002
IV 7S	4.4 (3.7, 5.2)	4.0 (3.5, 4.9)	0.035	5.3 (4.4, 6.1)	4.4 (3.8, 5.4)	0.123	7.2 (5.7, 8.9)	5.7 (4.2, 6.7)	0.020	8.6 (7.0, 11.0)	5.8 (5.0, 7.1)	0.000
P3P, U/ml	0.79 (0.66, 0.90)	0.58 (0.50, 0.70)	0.000	0.80 (0.71, 1.00)	0.84 (0.65, 0.94)	0.698	1.05 (0.83, 1.30)	0.63 (0.48, 0.81)	0.001	1.10 (0.90, 1.30)	0.63 (0.51, 0.77)	0.000
MMP3, ng/ml	37.7 (25.6, 58.1)	36.7 (21.2, 46.0)	0.217	34.3 (27.0, 50.4)	51.3 (28.0, 64.1)	0.177	40.2 (24.6, 52.7)	62.9 (37.7, 80.7)	0.030	39.0 (32.5, 55.9)	41.1 (28.5, 51.1)	0.542

Values are presented as median (first quartile, third quartile). The p values were calculated with the Mann-Whitney U test.