Oncology

Clinical Study

C-Reactive Protein and Platelet-Lymphocyte Ratio as Potential Tumor Markers in Low-Alpha-Fetoprotein Hepatocellular Carcinoma

Suner A.[a] · Carr B.I.[b] · Akkiz H.[c] · Karakülah G.[b,d] · Üsküdar O.[c] · Yalçın K.[e] · Kuran S.[c] · Tokat Y.[c] · Yilmaz S.[b] · Özakyol A.[f] · Tokmak S.[c] · Ballı T.[c] · Yücesoy M.[g] · Bahçeci H.İ.[h] · Ülkü A.[c] · Akçam T.[c] · Polat K.Y.[i] · Ekinci N.[e] · Şimşek H.[j] · Örmeci N.[k] · Sonsuz A.[l] · Demir M.[m] · Kılıç M.[n] · Uygun A.[o] · Demir A.[p] · Delik A.[c] · Arslan B.[c] · Doran F.[c] · Altıntaş E.[q] · Temel T.[r] · Bektaş A.[s]
Author affiliations

Keywords: C-reactive protein · Platelet-lymphocyte ratio · Neutrophil-lymphocyte ratio · Hepatocellular carcinoma · Aggressiveness

---

Oncology 2019;96:25–32
https://doi.org/10.1159/000492473

Abstract | Get article | FullText | PDF | Login / Register

Abstract

The hepatocellular carcinoma (HCC) tumor marker alpha-fetoprotein (AFP) is only elevated in about half of the HCC patients, limiting its usefulness in following the effects of therapy or screening. New markers are needed. It has been previously noted that the inflammation markers C-reactive protein (CRP) and platelet-lymphocyte ratio (PLR) are prognostically important and may reflect HCC aggressiveness. We therefore examined these 2 markers in a low-AFP HCC cohort and found that for HCCs > 2 cm, both markers significantly rise with an increasing maximum tumor diameter (MTD). We calculated the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and Youden index value for each marker, and their area-under-the-curve values for each MTD group. Patients were dichotomized into 2 groups based on the CRP and PLR from the receiver-operating characteristic curve analysis. In the logistic regression models of the 4 different MTD patient groups, CRP and PLR levels were statistically significant to estimate MTD in univariate logistic regression models of MTD groups > 2 cm. CRP and PLR were then combined, and the combination was statistically significant to estimate MTD groups of 3-, 4-, and 5-cm cutoffs. CRP and PLR thus have potential as tumor markers for low-AFP HCC patients, and possibly for screening.

Related Articles:

Liver Cancer

Liver Cancer 2018;7:1–224

9th Asia-Pacific Primary Liver Cancer Expert Meeting, Seoul, South Korea, July 6-8, 2018

Go to Article

Liver Cancer

Liver Cancer 2013;2:153–331

The 4th Asia-Pacific Primary Liver Cancer Expert Meeting

Go to Article

Liver Cancer

Liver Cancer 201

The 5th Asia
Liver Cance
(APPLE 2014
Consensus o
Managemen
Taiwan, July
Abstracts

Go to Article

References

1. Bai DS, Zhang C, Chen P, Jin SJ, Jiang GQ. The prognostic correlation of AFP level at diagnosis with pathological grade, progression, and survival of patients with hepatocellular carcinoma. Sci Rep. 2017 Oct;7(1):12870.
   External Resources
- Crossref (DOI)
- Pubmed/Medline (NLM)

2. Carr BI, Akkiz H, Üsküdar O, Yalçın K, Guerra V, Kuran S, et al. HCC with low- and normal-serum alpha-fetoprotein levels [Lond]. Clin Pract (Lond). 2018;15(1):453–64.
   External Resources
- Pubmed/Medline (NLM)

3. Jing JS, Ye W, Jiang YK, Ma J, Zhu MQ, Ma JM, et al. The Value of GPC3 and GP73 in Clinical Diagnosis of Hepatocellular Carcinoma. Clin Lab. 2017 Nov;63(11):1903–9.
   External Resources
- Pubmed/Medline (NLM)

4. Kobayashi T, Itamoto T, Tashiro H, Amano H, Oshita A, Tanimoto Y, et al. Tumor-related factors do not influence the prognosis of solitary hepatocellular carcinoma after partial hepatectomy. J Hepatobiliary Pancreat Sci. 2011 Sep;18(5):689–99.

External Resources

- Pubmed/Medline (NLM)
- Crossref (DOI)

5. Chan SL, Chan AW, Chan AK, Jian P, Mo F, Chan CM, et al. Systematic evaluation of circulating inflammatory markers for hepatocellular carcinoma. Liver Int. 2017 Feb;37(2):280–9.

External Resources

- Pubmed/Medline (NLM)
- Crossref (DOI)

6. Wang X, Hassan W, Jabeen Q, Khan GJ, Iqbal F. Interdependent and independent multidimensional role of tumor microenvironment on hepatocellular carcinoma. Cytokine. 2018 Mar;103:150-59.

External Resources

- Crossref (DOI)

7. Novikova MV, Khromova NV, Kopnin PB. Components of the Hepatocellular Carcinoma Microenvironment and Their Role in Tumor Progression [Mosc]. Biochemistry (Mosc). 2017 Aug;82(8):861–73.

External Resources

- Pubmed/Medline (NLM)
- Crossref (DOI)

8. Toniatti C, Arcone R, Majello B, Ganter U, Arpaia G, Ciliberto G. Regulation of the human C-reactive protein gene, a major marker of inflammation and cancer [Review]. Mol Biol Med. 1990 Jun;7(3):199–212.

External Resources

- Pubmed/Medline (NLM)

9. Fabris C, Pirisi M, Soardo G, Toniutto P, Falleti E, Vitulli D, et al. Diagnostic usefulness of acute-phase protein measurement in hepatocellular carcinoma. Cancer Invest. 1996;14(2):103–8.

External Resources

- Pubmed/Medline (NLM)
- Crossref (DOI)

10. Hashimoto K, Ikeda Y, Korenaga D, Tanoue K, Hamatake M, Kawasaki K, et al. The impact of preoperative serum C-reactive protein on the prognosis of patients with hepatocellular carcinoma. Cancer. 2005 May;103(9):1856–64.

External Resources

- Pubmed/Medline (NLM)
- Crossref (DOI)

11. Sieghart W, Pinter M, Hucke F, Graziadei I, Schöniger-Hekele M, Müller C, et al. Single determination of C-reactive protein at the time of diagnosis predicts long-term outcome of patients with hepatocellular carcinoma. Hepatology. 2013 Jun;57(6):2224–34.

External Resources

- Pubmed/Medline (NLM)
- Crossref (DOI)

12. Li X, Chen ZH, Ma XK, Chen J, Wu DH, Lin Q, et al. Neutrophil-to-lymphocyte ratio acts as a prognostic factor for patients with advanced hepatocellular carcinoma. Tumour Biol. 2014 Nov;35(11):11057–63.

External Resources

- Pubmed/Medline (NLM)
- Crossref (DOI)

13. Kinoshita A, Onoda H, Imai N, Iwaku A, Oishi M, Fushiya N, et al. Comparison of the prognostic value of inflammation-based prognostic scores in patients with hepatocellular carcinoma. Br J Cancer. 2012 Sep;107(6):988–93.

External Resources

- Pubmed/Medline (NLM)
- Crossref (DOI)

14. Aino H, Sumie S, Niizeki T, Kuromatsu R, Tajiri N, Nakano M, et al. The systemic inflammatory response as a prognostic factor for advanced hepatocellular carcinoma with extrahepatic metastasis. Mol Clin Oncol. 2016 Jul;5(1):83–8.

External Resources

- Pubmed/Medline (NLM)
- Crossref (DOI)

15. Zhao Y, Si G, Zhu F, Hui J, Cai S, Huang C, et al. Prognostic role of platelet to lymphocyte ratio in hepatocellular carcinoma: a systematic review and meta-analysis. Oncotarget. 2017 Apr;8(14):22854–62.

External Resources

- Pubmed/Medline (NLM)
- Crossref (DOI)

16. Ma W, Zhang P, Qi J, Gu L, Zang M, Yao H, et al. Prognostic value of platelet to lymphocyte ratio in hepatocellular carcinoma: a meta-analysis. Sci Rep. 2016 Oct;6(1):35378.

External Resources

- Pubmed/Medline (NLM)
- Crossref (DOI)

17. Chen K, Zhan MX, Hu BS, Li Y, He X, Fu SR, et al. Combination of the neutrophil to lymphocyte ratio and the platelet to lymphocyte ratio as a useful predictor for recurrence following radiofrequency ablation of hepatocellular carcinoma. Oncol Lett. 2018 Jan;15(1):315–23.

External Resources

- Pubmed/Medline (NLM)

18. Carr BI, Akkiz H, Guerra V, Üsküdar O, Kuran S, Karaoğullarından Ü, et al. C-reactive protein and hepatocellular carcinoma: analysis of its relationships to tumor factors [Therapy]. Clin Pract (Lond). 2018;15(Spec Issue):625–34.

External Resources

- Pubmed/Medline (NLM)
- Crossref (DOI)

19. Metz CE. Basic principles of ROC analysis. Semin Nucl Med. 1978 Oct;8(4):283–98.

External Resources

- Pubmed/Medline (NLM)
- Crossref (DOI)

20. Fluss R, Faraggi D, Reiser B. Estimation of the Youden Index and its associated cutoff point. Biom J. 2005 Aug;47(4):458–72.

External Resources

- Pubmed/Medline (NLM)
- Crossref (DOI)

21. Shrotriya S, Walsh D, Bennani-Baiti N, Thomas S, Lorton C. T homas S, Lorton C. C-Reactive Protein is an important biomarker for prognosis tumor recurrence and treatment response in adult solid tumors: a systematic review. PLoS One. 2015 Dec;10(12):e0143080.

External Resources

- Pubmed/Medline (NLM)
- Crossref (DOI)

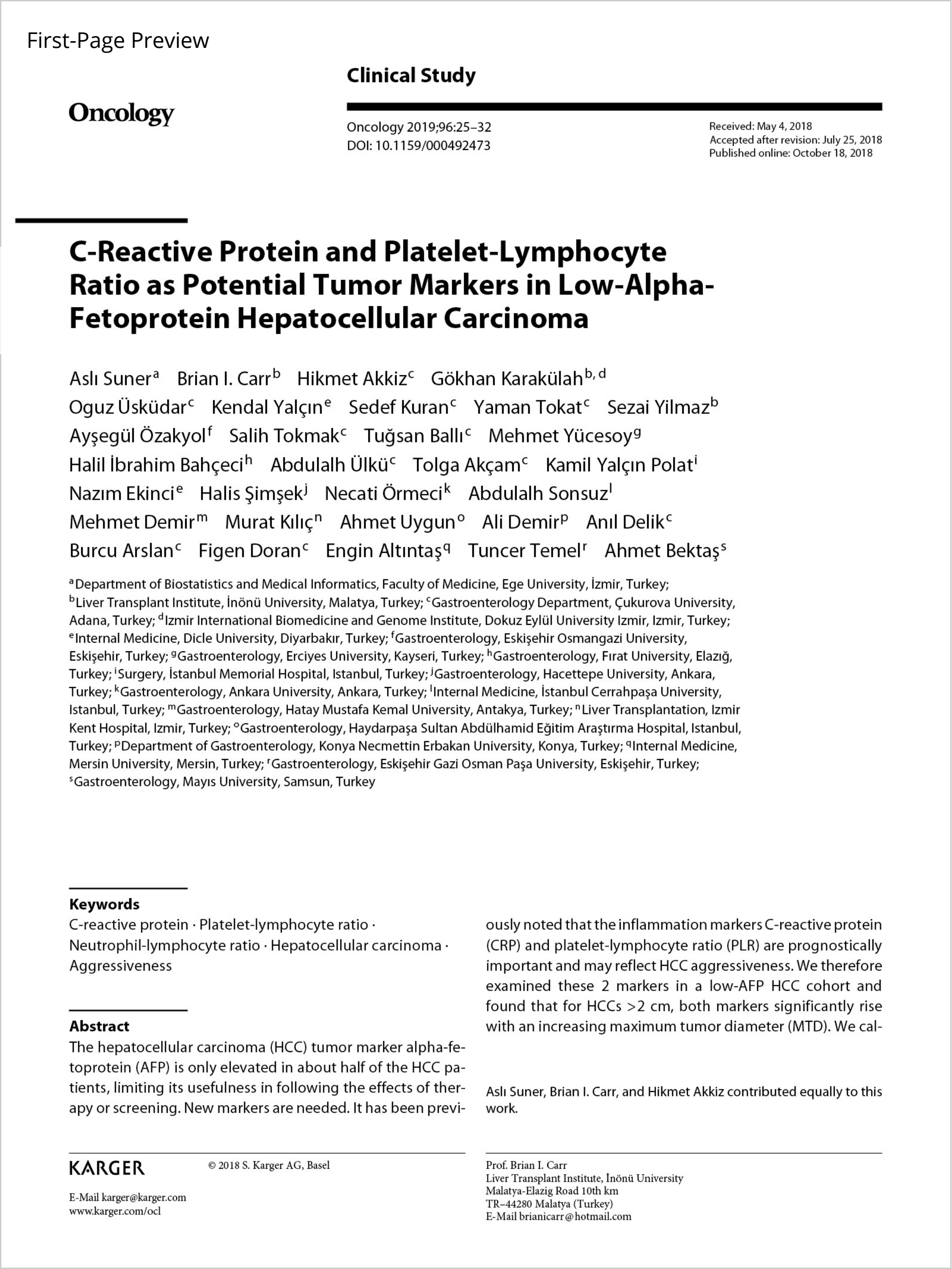
22. Bihari C, Rastogi A, Shasthry SM, Bajpai M, Bhadoria AS, Rajesh S, et al. Platelets contribute to growth and metastasis in hepatocellular carcinoma. APMIS. 2016 Sep;124(9):776–86.
External Resources
- Pubmed/Medline (NLM)
- Crossref (DOI)

23. Carr BI, Cavallini A, D'Alessandro R, Refolo MG, Lippolis C et al. Platelet extracts induce growth, migration and invasion in human hepatocellular carcinoma in vitro. BMC Cancer. 2014 Jan;14:43.

24. He AD, Xie W, Song W, Ma YY, Liu G, Liang ML, et al. Platelet releasates promote the proliferation of hepatocellular carcinoma cells by suppressing the expression of KLF6. Sci Rep. 2017 Jun;7(1):3989.
External Resources
- Pubmed/Medline (NLM)
- Crossref (DOI)

25. Suner A, Carr BI, Akkiz H, Uskudar O, Kuran S, et al. Inflammatory markers C- reactive protein and PLR in relation to HCC tumor characteristics. J Transl Sci. 2018;5(3):1–6.
External Resources
- Crossref (DOI)

Article / Publication Details



Clinical Study

Oncology

Oncology 2019;96:25–32
DOI: 10.1159/000492473

Received: May 4, 2018
Accepted after revision: July 25, 2018
Published online: October 18, 2018

C-Reactive Protein and Platelet-Lymphocyte Ratio as Potential Tumor Markers in Low-Alpha-Fetoprotein Hepatocellular Carcinoma

Aslı Suner[a] Brian I. Carr[b] Hikmet Akkiz[c] Gökhan Karakülah[b, d] Oguz Üsküdar[c] Kendal Yalçın[e] Sedef Kuran[c] Yaman Tokat[c] Sezai Yilmaz[b] Ayşegül Özakyol[f] Salih Tokmak[c] Tuğsan Ballı[c] Mehmet Yücesoy[g] Halil İbrahim Bahçeci[h] Abdulalh Ülkü[c] Tolga Akçam[c] Kamil Yalçın Polat[i] Nazım Ekinci[e] Halis Şimşek[j] Necati Örmeci[k] Abdulalh Sonsuz[l] Mehmet Demir[m] Murat Kılıç[n] Ahmet Uygun[o] Ali Demir[p] Anıl Delik[c] Burcu Arslan[c] Figen Doran[c] Engin Altıntaş[q] Tuncer Temel[r] Ahmet Bektaş[s]

[a]Department of Biostatistics and Medical Informatics, Faculty of Medicine, Ege University, İzmir, Turkey; [b]Liver Transplant Institute, İnönü University, Malatya, Turkey; [c]Gastroenterology Department, Çukurova University, Adana, Turkey; [d]Izmir International Biomedicine and Genome Institute, Dokuz Eylül University Izmir, Izmir, Turkey; [e]Internal Medicine, Dicle University, Diyarbakır, Turkey; [f]Gastroenterology, Eskişehir Osmangazi University, Eskişehir, Turkey; [g]Gastroenterology, Erciyes University, Kayseri, Turkey; [h]Gastroenterology, Fırat University, Elazığ, Turkey; [i]Surgery, İstanbul Memorial Hospital, Istanbul, Turkey; [j]Gastroenterology, Hacettepe University, Ankara, Turkey; [k]Gastroenterology, Ankara University, Ankara, Turkey; [l]Internal Medicine, İstanbul Cerrahpaşa University, Istanbul, Turkey; [m]Gastroenterology, Hatay Mustafa Kemal University, Antakya, Turkey; [n]Liver Transplantation, Izmir Kent Hospital, Izmir, Turkey; [o]Gastroenterology, Haydarpaşa Sultan Abdülhamid Eğitim Araştırma Hospital, Istanbul, Turkey; [p]Department of Gastroenterology, Konya Necmettin Erbakan University, Konya, Turkey; [q]Internal Medicine, Mersin University, Mersin, Turkey; [r]Gastroenterology, Eskişehir Gazi Osman Paşa University, Eskişehir, Turkey; [s]Gastroenterology, Mayıs University, Samsun, Turkey

Keywords

C-reactive protein · Platelet-lymphocyte ratio · Neutrophil-lymphocyte ratio · Hepatocellular carcinoma · Aggressiveness

Abstract

The hepatocellular carcinoma (HCC) tumor marker alpha-fetoprotein (AFP) is only elevated in about half of the HCC patients, limiting its usefulness in following the effects of therapy or screening. New markers are needed. It has been previously noted that the inflammation markers C-reactive protein (CRP) and platelet-lymphocyte ratio (PLR) are prognostically important and may reflect HCC aggressiveness. We therefore examined these 2 markers in a low-AFP HCC cohort and found that for HCCs >2 cm, both markers significantly rise with an increasing maximum tumor diameter (MTD). We cal-

Aslı Suner, Brian I. Carr, and Hikmet Akkiz contributed equally to this work.

E-Mail karger@karger.com
www.karger.com/ocl

Prof. Brian I. Carr
Liver Transplant Institute, İnönü University
Malatya-Elazig Road 10th km
TR–44280 Malatya (Turkey)
E-Mail brianicarr@hotmail.com

Received: May 04, 2018
Accepted: July 25, 2018
Published online: October 18, 2018
Issue release date: December 2018

Number of Print Pages: 8
Number of Figures: 0
Number of Tables: 5

ISSN: 0030-2414 (Print)
eISSN: 1423-0232 (Online)

For additional information: https://www.karger.com/OCL

Copyright / Drug Dosage / Disclaimer

Copyright: All rights reserved. No part of this publication may be translated into other languages, reproduced or utilized in any form or by any means, electronic or mechanical, including photocopying, recording, microcopying, or by any information storage and retrieval system, without permission in writing from the publisher.
Drug Dosage: The authors and the publisher have exerted every effort to ensure that drug selection and dosage set forth in this text are in accord with current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert for each drug for any changes in indications and dosage and for added warnings and precautions. This is particularly important when the recommended agent is a new and/or infrequently employed drug.
Disclaimer: The statements, opinions and data contained in this publication are solely those of the individual authors and contributors and not of the publishers and the editor(s). The appearance of advertisements or/and product references in the publication is not a warranty, endorsement, or approval of the products or services advertised or of their effectiveness, quality or safety. The publisher and the editor(s) disclaim responsibility for any injury to persons or property resulting from any ideas, methods, instructions or products referred to in the content or advertisements.

English Language Editing and Manuscript Preparation Services

Get 10% OFF with KARGER discount

AJE

Learn More

ONCOLOGY

at KARGER