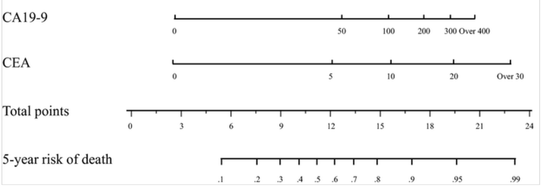
Original Scientific Report

Prognostic Utility of the Geneva Prognostic Score for the Long-Term Outcomes After Lower Resection for Intrapelvic Cholangiocarcinoma: A Multi-Institutional Study

Yoshio Mizuno[1], Takehiro Okabayashi[2], Yosuke Fukami[3], Gouki Okazaki[4], Yoshifumi Takeda[5], Satoru Seo[6], Kazunori Akimaru[7], Masaru Miyazaki[8], Yoichi Matsuo[9], Masao Tanaka[10], Masato Nagino[11], Masayuki Ohzato[12], Takashi Sugimoto[13], Takayuki Anazawa[14], Yasuhisa Mizushima[15], Yasuhiro Shimizu[16], Masaki Ueno[17], Hiroki Hara[18], Yuichiro Doi[19], Yasushi Rino[20], Masashi Yamanaka[21], Yasuhiro Shimada[22], Masahiko Watanabe[23], Hiroyuki Bando[24], Yuichiro Yeh[25], Masaki Kaneko[26], Akihiro Yamamoto[27], Yuichiro Tsuchikawa[28], Tetsuya Abe[29], Masahiro Shinoda[30], Masayuki Ohue[31], Yuichiro Tanaka[32], Yuichiro Doki[33], Masaki Mori[34], Hiroshi Wada[35], Masahiro Tanemura[36], Hiroaki Nagano[37], Masayuki Ohzato[38], Masaki Kaneko[39], Masaki Ueno[40], Masaki Mori[41], Yuichiro Doki[42], Masahiro Tanemura[43], Hiroaki Nagano[44], Masayuki Ohzato[45], Masaki Kaneko[46], Masaki Ueno[47], Masaki Mori[48], Yuichiro Doki[49], Masahiro Tanemura[50], Hiroaki Nagano[51], Masayuki Ohzato[52], Masaki Kaneko[53], Masaki Ueno[54], Masaki Mori[55], Yuichiro Doki[56], Masahiro



Discussion

This study demonstrated that the GPS (calculated from preoperative serum albumin and CRP levels) can help predict ICC patient survival after a curative resection. The GPS is a known prognostic factor for various cancers and is frequently an indicator of tumour size, TNM classification, and lymph node metastasis [16, 17]. Therefore, to eliminate the effect of other prognostic factors, the cohort in the present study was matched for four factors: tumour size, CA19-9 level, anatomic location of the primary cancer, and extra hepatic bile duct resection, all of which were prognostic factors on univariate analysis for OS and were associated with the GPS. Upon propensity score matching, the GPS showed itself to be a prognostic independent factor under multivariate analysis. As far as we are aware, this large-scale cohort study is the first to show that the GPS is an independent prognostic factor for ICC patients [18].

Cancer is a complex disease due to the cells intrinsic and extrinsic processes [19]. Systemic inflammation along with malnutrition status are well-established factors that are correlated with a poor prognosis in various tumours. The proliferation, angiogenesis, and metastasis of a tumour are closely associated with its related inflammation responses [20]. CRP, an acute phase protein thought to be a predictor of infection, is induced by pro-inflammatory cytokines after being synthesized in the liver. Elevated CRP levels can also be seen during tumour metastasis. Albumin, a protein that circulates in the plasma, can additionally be part of the inflammatory response. Therefore, the GPS may be an indicator of the potential inflammatory status in the body. Furthermore, both inflammation and malnutrition are known to associate with a lower quality of life as well as having negative effects on the treatment effectiveness of patients with cancer [21]. The GPS can show the inflammatory and nutritional status of patients during their treatment as a variable that can be quantified continuously. This study shows that a higher GPS can be a useful and remarkable predictor of poorer OS in ICC patients who underwent a liver resection.

On multivariate analysis after propensity score matching, positive metastasis to the lymph nodes and histopathological undifferentiated carcinoma were both independent pathological prognostic factors. However, these factors were only available from specimens obtained after resection. An evaluation before surgical treatment is essential, and it is important to make a diagnosis based on preoperative information about the ICC, especially because some investigators assert that ICC is a systemic disease and should be treated with systemic therapy [22]. We believe that patients with ICC are at high risk of poor outcomes after medical management and should be identified using simple baseline clinical and laboratory parameters. Accordingly, the results here show that high GPS patients might need adjuvant therapy to increase the chance of prolonging life expectancy even though surgery is the only potential curative treatment for localized biliary tract cancer [23].

The cohort sample size was a factor which limits our subgroup analyses but was well-characterized and diverse considering the associations between the key prognostic factor, i.e. the GPS, and the long-term outcomes after surgical treatment for patients with ICC. Some other limitations in the study included the retrospective nature of the work and the fact that the patients were enrolled from multiple institutions in Japan, where the risk factors are different from those of patients in Western countries considering the carcinogenesis of ICC [24]. In addition, we did not analyse the change in trends of postoperative GPS, because the follow-up protocol was different between participating facilities. Moreover, patients who had underwent a curative resection were the only ones included in our study. A convalescence nomogram of the ICC was established by the combination of GPS, CEA, and CA19-9. This nomogram was highly predictive, similar to the classification system for conventional TNM stages of ICC. Nevertheless, despite the aforementioned limits, the finding of this study focuses on the protocol design and most suitable allocation of the treatment plan based on the individual characteristics of each ICC patient.

To date, the prognosis for ICC uses the complex pathological TNM classification and is postoperatively assessed. The GPS system is a biochemically simple test using preoperative serum CRP and albumin levels. This study showed that GPS, a novel and easily administered inflammation examination, had strong prognostic capability for ICC patients who underwent a curative resection. A high GPS is a negatively correlated biomarker for the overall survival of ICC patients after a hepatectomy. Accordingly, using the GPS to improve the accuracy of the preoperative prognosis may aid in the appropriate selection of patients for surgical treatment.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Acknowledgements

The authors thank their colleagues who contributed to data collection for this study: Kazuyasu Kobayashi (Sumitomo Besshi Hospital), Toshihiro Murata (Onomichi Municipal Hospital), Hideki Aoki (National Iwakuni Medical Center), Yasuhiko Ishida (Himeji Central Hospital), and Nobuhiro Ishido (Kobe Red Cross Hospital). The authors wish to thank Dr. Tomokazu Fuji and Kazuhiro Yoshida for giving technical assistance ~~and Editage~~ ~~for English language editing~~.

Funding

This study was financially supported by the Japan Society for the Promotion of Science (JSPS), Grant Number 19K09217 to Yuzo Umeda.

Compliance with ethical standards

Conflict of interest The author declares that they have no conflict of interest.

References

1. Bray F, Ferlay J, Soerjomataram I et al (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68:394–424

2. Alpini G, Prall R, LaRusso NF (2001) The pathobiology of biliary epithelia. In: Arias IM, Boyer JL, Chisari FV, et al. (eds) The liver biology and pathobiology, 4th edn. Lippincott Williams & Wilkins, Philadelphia

3. Satriano L, Lewinska M, Rodrigues PM et al (2019) Metabolic rearrangements in primary liver cancers: cause and consequences. Nat Rev Gastroenterol Hepatol 16:748–766

4. Okabayashi T, Yamamoto J, Kosuge T et al (2001) A new staging system for mass-forming intrahepatic cholangiocarcinoma: analysis of preoperative and postoperative variables. Cancer 92:2374–2383

5. Schnitzbauer AA, Eberhard J, Bartsch F et al (2019) The MEGNA score and preoperative anemia are major prognostic factors after resection in the German intrahepatic cholangiocarcinoma cohort. Ann Surg Oncol. https://doi.org/10.1245/s10434-019-07968-7

6. Wang Y, Li J, Xia Y et al (2013) Prognostic nomogram for intrahepatic cholangiocarcinoma after partial hepatectomy. J Clin Oncol 31:1188–1195

7. Massarweh NN, El-Serag HB (2017) Epidemiology of hepatocellular carcinoma and intrahepatic cholangiocarcinoma. Cancer Control 24:1073274817729245

8. Sharaiha RZ, Halazun KJ, Mirza F et al (2011) Elevated preoperative neutrophil: lymphocyte ratio as a predictor of postoperative disease recurrence in esophageal cancer. Ann Surg Oncol 18:3362–3369

9. Chan JC, Chan DL, Diakos CI et al (2017) The lymphocyte-to-monocyte ratio is a superior predictor of overall survival in comparison to established biomarkers of resectable colorectal cancer. Ann Surg 265:539–546

10. Mano Y, Shirabe K, Yamashita Y et al (2013) Preoperative neutrophil-to-lymphocyte ratio is a predictor of survival after hepatectomy for hepatocellular carcinoma: a retrospective analysis. Ann Surg 258:301–305

11. Okabayashi T, Shima Y, Sumiyoshi T et al (2018) A Novel physiobiological parameter-based grading system for resectable pancreatic cancer. Ann Surg Oncol 25:1889–1895

12. Ishii Y, Sasaki T, Serikawa M et al (2013) Elevated expression of cyclooxygenase-2 and microsomal prostaglandin E synthase-1 in primary sclerosing cholangitis: iotamplications for cholangiocarcinogenesis. Int J Oncol 43:1073–1079

13. Lin G, Liu Y, Li S et al (2016) Elevated neutrophil-to-lymphocyte ratio is an independent poor prognostic factor in patients with intrahepatic cholangiocarcinoma. Oncotarget 7:50963–50971

14. Ohira M, Yoshizumi T, Yugawa K et al (2019) Association of inflammatory biomarkers with long-term outcomes after curative surgery for mass-forming intrahepatic cholangiocarcinoma. Surg Today. https://doi.org/10.1007/s00595-019-01905-7

15. McMillan DC (2008) An inflammation-based prognostic score and its role in the nutrition-based management of patients with cancer. Proc Nutr Soc 67:257–262

16. Dolan RD, Almasaudi AS, Dieu LB et al (2019) The relationship between computed tomography-derived body composition, systemic inflammatory response, and survival in patients undergoing surgery for colorectal cancer. J Cachexia Sarcopenia Muscle 10:111–122

17. Reeh M, Ghadban T, Uzunoglu FG et al (2017) Hamburg-Glasgow classification: preoperative staging by combination of disseminated tumour load and systemic inflammation in oesophageal carcinoma. Br J Cancer 117:612–618

18. Pan QX, Su ZJ, Zhang JH et al (2017) Glasgow prognostic score predicts prognosis of intrahepatic cholangiocarcinoma. Mol Clin Oncol 6:566–574

19. Antonioli L, Blandizzi C, Pacher P et al (2013) Immunity, inflammation and cancer: a leading role for adenosine. Nat Rev Cancer 13:842–857

20. Mantovani A, Allavena P, Sica A et al (2008) Cancer-related inflammation. Nature 454:436–444

21. Rogers PC (2014) Nutritional status as a prognostic indicator for pediatric malignancies. J Clin Oncol 32:1293–1294

22. Lamarca A, Barriuso J, McNamara MG et al (2018) Biliary tract cancer: state of the art and potential role of DNA damage repair. Cancer Treat Rev 70:168–177

23. Primrose JN, Fox RP, Palmer DH,: BILCAP study group, et al (2019) Capecitabine compared with observation in resected biliary tract cancer (BILCAP): a randomised, controlled, multicentre, phase 3 study. Lancet Oncol 20:663–673

24. Bridgewater J, Galle PR, Khan SA et al (2014) Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. J Hepatol 60:1268–1289