

# Letter to the Editor

## Comment on “Research on values of GDF-15 level in the diagnosis of primary liver cancer and evaluation of chemotherapeutic effect”

Dear Editor,

We read with great interest the original paper by Shen et al<sup>1</sup> about “Research on values of GDF-15 level in the diagnosis of primary liver cancer and evaluation of chemotherapeutic (CT) effect”. Primary liver cancer represents the most common primary cancer and despite the advances in oncological and surgical treatments, hepatocellular carcinoma (HCC) is still a global burden, representing the third cancer-related cause of death worldwide<sup>2-5</sup>. The objective of the authors was to investigate the values of growth differentiation factor-15 (GDF-15) level in the diagnosis of primary liver cancer and evaluation of chemotherapeutic effect. According to English literature we know that GDF-15 is a member of the transforming growth factor  $\beta$  (TGF- $\beta$ ) superfamily. It has been verified as a regulator in a variety of biological processes and cellular functions, such as cell apoptosis, differentiation and proliferation. Recently, multiple studies reported that GDF-15 was elevated in several cancers, including pancreatic ductal adenocarcinoma, endometrial cancer, colorectal cancer and gastric cancer. The expression of GDF-15 in tumor tissues and effusion was negatively correlated with the survival of ovarian cancer. Moreover, its over-expression promoted tumorigenesis of prostate carcinoma cells. Regarding the HCC, serum GDF-15 level was significantly increased in patients with HCC and GDF-15 could be served as a serum biomarker in HCC<sup>6</sup>. The early diagnosis of liver cancer represents a crucial aspect to improving the treatment effect on liver cancer and prolonging overall survival of patients and it is well known that a multidisciplinary panel should provide a tailored approach for each patient, considering both guideline indications and patient-specific characteristics, enhancing the hospital-specific best practice. In this context the serum value of GDF-15 could have a decisive role for differential diagnosis between primary liver cancer and benign lesion and to evaluate the response to CT. The authors reported different results about the values of serum GDF-15 level between 92 patients with primary liver cancer and a control group with benign liver disease, evidencing significant differences between two groups with higher value in primary liver cancer. Moreover, the GDF-15 value is directly related to stage of primary liver cancer. In the next future is desirable that the contemporary use of GDF-15, liver ultrasound, MRI or CT liver scanner and alpha-fetoprotein could improve the accuracy in primary liver cancer, especially at the initial stage and in differential diagnosis between benign and malignant liver lesion. Regarding the role about the response to treatment is interesting to observe that patients with progressive disease have higher serum GDF-15 level than those with partial remission and stable disease. Is this data super-imposable to serum AFP level in responder cancer patients? Moreover, we know that many serum tumor markers, such as Cea, Ca 19.9, Ca 125, Ca 15.3, Cromogranina A, Bhcg and PSA<sup>7,8</sup> can be influenced by non-malignant disease and could be interesting to know if GDF-15 is influenced by non malignant liver disease. In fact, Liu et al<sup>9</sup> found that GDF-15 expression is associated with the hepatitis-related liver disease and could be interesting to know if there are some differences in presence of malignant lesions and chronic or infection<sup>10</sup> liver disease. Have the authors tried the value of the serum GDF-15 in non-malignant liver disease? In conclusion, we think that this kind of study is important to improve the knowledge about early diagnosis for primary liver cancer and in a particular setting of patients such as those in CT treatment to evaluate the response to treatment.

### Conflict of interest

The authors declare no conflicts of interest.

### References

- 1) SHEN Y, ZHANG ZB, WU SD, WU XB, LI J. Research on values of GDF-15 level in the diagnosis of primary liver cancer and evaluation of chemotherapeutic effect. *Eur Rev Med Pharmacol Sci* 2018; 22: 3749-3754.
- 2) BERRETTA M, CAVALIERE C, ALESSANDRINI L, STANZIONE B, FACCHINI G, BALESTRERI L, PERIN T, CANZONIERI V. Serum and tissue markers in hepatocellular carcinoma and cholangiocarcinoma: clinical and prognostic implications. *Oncotarget* 2017; 8: 14192-14220.
- 3) BERRETTA M, RINALDI L, DI BENEDETTO F, LLESHI A, DE RE V, FACCHINI G, DE PAOLI P, DI FRANCA R. Angiogenesis inhibitors for the treatment of hepatocellular carcinoma. *Front Pharmacol* 2016; 7: 428.
- 4) MOHAMMADIAN M, MAHDAVIFAR N, MOHAMMADIAN-HAFSHEJANI A, SALEHINIYA H. Liver cancer in the world: epidemiology, incidence, mortality and risk factors. *WCRJ* 2018; 5: e1082.
- 5) BERRETTA S, FISICHELLA R, SPARTÀ D, LLESHI A, NASTI G. Primary liver cancer: clinical aspects, prognostic factors and predictive response to therapy. *WCRJ* 2015; 2: e561.
- 6) WANG L, LIU Y, LI W, SONG Z. Growth differentiation factor 15 promotes cell viability, invasion, migration, and angiogenesis in human liver carcinoma cell line HepG2. *Clin Res Hepatol Gastroenterol* 2017; 41: 408-414.
- 7) CANZONIERI V, ALESSANDRINI L, CAGGIARI L, PERIN T, BERRETTA M, CANNIZZARO R, DE RE V. Hepatocellular carcinoma: an overview of clinico-pathological and molecular perspectives. *WCRJ* 2015; 2: e485.
- 8) BIONDI A, MALAGUARNERA G, VACANTE M, BERRETTA M, D'AGATA V, MALAGUARNERA M, BASILE F, DRAGO F, BERTINO G. Elevated serum levels of Chromogranin A in hepatocellular carcinoma. *BMC Surg* 2012; 12 Suppl 1: S7.
- 9) LIU X, CHI X, GONG Q, GAO L, NIU Y, CHI X, CHENG M, SI Y, WANG M, ZHONG J, NIU J, YANG W. Association of serum level of growth differentiation factor 15 with liver cirrhosis and hepatocellular carcinoma. *PLoS One* 2015; 10: e0127518.
- 10) ADINOLFI LE, NEVOLA R, RINALDI L, ROMANO C, GIORDANO M. Chronic hepatitis C virus infection and depression. *Clin Liver Dis* 2017; 21: 517-534.

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