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Healthy Male Individuals Possess Higher Plasma HER-2 Level than Females

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Abstract

Considering HER2 as one of the well-known biomarkers in the cancer field, and published articles regarding serum levels of HER2, in this paper we tried to highlight the issue that most studies don't stratify the HER-2 concentration of individuals in terms of gender. In this brief survey, healthy individuals with no prior non-communicable diseases were categorized as males (n=34) and females (n=43), and all samples were evaluated for plasma HER-2 levels at once. Surprisingly, the plasma level of HER-2 of healthy male individuals (mean= 2.28 ± 0.21 ng/mL) was significantly (P<0.0001) higher than the plasma level of HER-2 of healthy females (mean: 0.06 ± 0.09 ng/mL), with no overlap. Therefore, we suggest that more studies are required to re-check the cutoff values for HER-2 plasma levels based on gender since the clinical implications of a unique HER-2 cutoff for both genders may be seriously concerning.

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The overexpression of human epidermal growth factor receptor 2 (HER-2) has been reported in cancers including breast, gastric, gynecological, prostate, and pancreatic, also other diseases such as diabetes, and coronary artery disease, suggesting assessment of the level of HER-2 as an efficient diagnostic modality. Hence, the measurement of serum or plasma HER-2 level (1-4), along with Immunohistochemistry and Fluorescence In-Situ Hybridization (FISH) techniques is a growing field aimed to secure an accurate and less invasive approach for prognostic, diagnostic, and follow-up purposes. Recently, the importance of HER2-low and ultra-low positivity has been highlighted to transform the traditional binary HER2 scoring system (5-7). Patients with a low or very low level of HER2 expression are candidates for anti-HER2 antibody-drug conjugates therapies (5, 7, 8). It has been shown that the expression of HER-2 is regulated by various factors such as estrogen receptor, estradiol, progesterone, and sex-hormone profile which is expressed differently in males and females (9-13). Consequently, due to the physiological differences in males and females, a gender-related difference in HER-2 expression is expected. Therefore, we aimed to determine the significance of gender, as one of the most effective factors in the plasma level of HER-2.

We systematically searched for the studies from 2000 to 2021 in MEDLINE concerning the serum level of HER-2 or HER-2 ECD (extracellular domain) in different diseases compared to the control group (Supplementary Materials 1 and 2, See Supplementary Online Information at www.celljournal.org). Interestingly, 73.6% of included studies (n=19) were divided neither the patients nor the control group based on their gender regarding the HER-2 or HER-2 ECD serum level. However, a specified cutoff value for serum levels of HER-2 regarding the gender of patients is still undetermined yet of great importance. In this sense, we compared the serum level of HER-2 in healthy males and females. Herein, robust evidence

on the difference in serum levels of HER-2 in males and females is provided.

In this brief survey, healthy individuals with no prior non-communicable diseases were categorized as males (n=34) and females (n=43), and all samples were evaluated with an ELISA for HER-2 level at once (Supplementary material 3, See Supplementary Online Information at www.celljournal.org).

The human real samples were kindly provided by medical diagnostic laboratories of Sina Hospital, Farmanieh Hospital, and Motamed Cancer Institute in accordance with the ethical principles and the national norms and standards for conducting Medical Research in Iran (IR.ACECR.IBCRC.REC.1400.018).

We accepted only samples in ages (the 30 seconds to 50 seconds) with a declaration of absence of other underlying diseases, especially diseases related to the immune system and acute or chronic inflammations, specific systemic diseases (rheumatology, endocrine, cardiovascular, etc.), no chemotherapy or radiotherapy in the last six months, and absence of pregnancy. Surprisingly, the plasma level of HER-2 of healthy male individuals (mean=2.28 ± 0.21 ng/mL) was significantly ($P<0.0001$) higher than the plasma level of HER-2 of healthy females (mean: 0.06 ± 0.09 ng/mL), with no overlap (Fig.1). Although reported very limitedly in few studies (14-16), similar results have not attracted significant attention before, and no further discussion on the underlying causes or implications is provided in the literature.

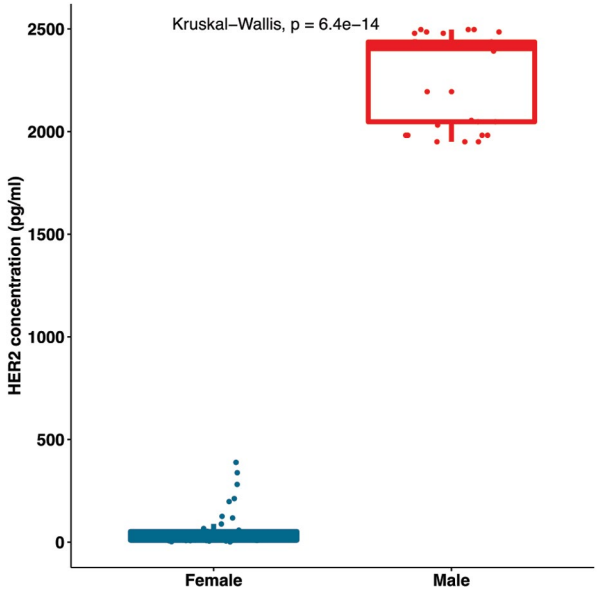

Fig.1: An Illustration of a comparison between serum HER2 level in plasma of healthy males and females (tested by sandwich ELISA procedure using prepared kit (invitrogen).

Clinical implications of the difference in HER-2 level between males and females:

We have observed that HER-2 plasma level is highly gender-related, and in healthy males is approximately 2-2.5 ng/ml, which is roughly 50 fold of the healthy female level. In the case of considering a cutoff value based on the general population, the HER-2 plasma level of perhaps all male individuals, either healthy or diseased one would be higher than the cutoff value; therefore, the prevalence of diseases screened by serum HER-2 may be overestimated in these individuals. The HER-2 plasma level may also differ between males and females in the patients' population; hence, male patients might have higher HER-2 levels due to their higher baseline HER-2 levels. The implications of this issue have been found significant in the interpretation of clinical data in some reports, although neglected by researchers (17-19). Through using average cutoff values, male and female patients might be over-treated and under-treated with HER-2-targeted therapies, respectively. Consequently, we strongly suggest more studies to define gender-specific cutoff values for HER-2 plasma levels in healthy and patient populations.

In conclusion, according to our observation, male individuals may have higher HER-2 plasma levels than females which might arise from the differences in sex hormones in males and females. The cutoff values for HER-2 plasma levels must be defined based on gender since the clinical implications of unique HER-2 cutoff for both genders such as overestimation and underestimation of diseases in males and females and inaccuracy of HER-2-targeted treatments are seriously concerning. However, more critical assessments are needed to find out if there were any nonspecific binding happened or the availability of gender-specific HER isoforms. Moreover, due to our limited group of studies, racial factors might also contribute to the observed difference in HER-2 plasma levels which necessitates similar investigations in other regions: with larger population involved.

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Authors' Contributions

S.T.F.; Formal analysis, Writing - original draft. A.B, F.Y.; Data curation, Visualization. L.G., A.O., S.M., R.S.F.; Resources, Methodology. A.S.N.; Funding acquisition, and Supervision. F.S.; Conceptualization, Methodology, Supervision. S.T.F., A.B., F.Y., L.G., A.O., S.M., R.S.F., A.S.N., F.S.; Writing - review and editing. All authors read and approved the final manuscript.

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