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Prognostic and Clinicopathological significance of CD155 Expression in Cancer Patients: A Meta-Analysis

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Review question / Objective: **The present study aimed to comprehensively explore the relationship between CD155 expression and clinical characteristics and prognosis of cancer patients. The study was based on comprehensive search of relevant literature. In particular, the study attempted to define the role of CD155 in various cancer types.**
Eligibility criteria: **The pre-established inclusion criteria were as follows: (1) all subjects were cancer patients who received standard treatment; (2) The expression of CD155 in the cancer patients was well-examined, and all patients were assigned into two groups based on the expression; (3) survival analysis was performed based on these two groups, and provided sufficient data to estimate the risk ratio (HR) and 95% confidence interval (CI) for overall survival (OS); and (4) scientific and reasonable research. Case reports, reviews, abstracts, letters, bioinformatic analysis, TCGA analysis, and articles that did not meet the inclusion criteria were excluded from analyses.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 18 September 2022 and was last updated on 18 September 2022 (registration number INPLASY202290086).

INTRODUCTION

Review question / Objective: **The present study aimed to comprehensively explore the relationship between CD155 expression and clinical characteristics and prognosis of cancer patients. The study was based on comprehensive search of relevant literature. In particular, the study attempted to define the role of CD155 in various cancer types.**

Rationale: **It has been previously reported that CD155 is often over-expressed in a variety of cancer types. In fact, it is known to be involved in cancer development, and its role in cancer has been widely established. However, clinical and**

mechanistic studies involving CD155 yielded conflicting results. Here, the present study aimed to comprehensively explore the relationship between CD155 expression and clinical characteristics and prognosis of cancer patients, thereby attempting to define the role of CD155 in various cancer types.

Condition being studied: Certain molecules have been previously shown to be barely expressed in most of the normal tissues; however, these molecules exhibited up-regulated expression in a variety of human malignancies, and played a vital role in cancer development. CD155 is one of these molecules, which is often over-expressed in cancer cells. It is known to be involved in various processes, such as cell adhesion, migration, proliferation, and tumor surveillance [5]. CD155 is also known as PVR, NECL-5, and TAGE-4, primarily owing to its different roles and attributions [6–8]. In particular, it has been previously shown that CD155 aggregates at the leading edge of migrating tumor cells, and co-locates with actin and αvβ3 integrin to promote cancer cell migration [9]. Cancer cell dispersal was found to be enhanced by up-regulation of CD155 expression, which recruited Src homology region 2 domain-containing phosphatase, and further potentiated focal adhesion kinase signaling [10]. Besides this, aberrant expression of CD155 could up-regulate cyclin D2, and shortened the G0/G1 phase. In comparison to this, down-regulated CD155 inhibited the proliferation of cancer cells and blocked the cell cycle at G2/M phase [11]. Additionally, previous studies reported that CD155 knockdown suppressed proliferation, and promoted apoptosis via AKT/Bcl-2/Bax [12]. Similarly, differential expression of CD155 might regulate PDGF-mediated cell proliferation, VEGF expression, and intratumoral vascular density [13, 14]. The role of CD155 in cancer has been verified in animal model experiments. Importantly, clinicopathological analysis concluded that CD155 over-expression was associated with poor prognosis of cancer patients [2, 3]. Altogether, these findings highlighted that CD155 played a physiological role as a pro-oncogenic molecule. However, accumulating evidences revealed that CD155 performed various other functions. In fact, it was reported that CD155 played a more complex role in tumor immunity and surveillance [15]. In particular, over-expression of CD155 in cancer is recognized by a group of receptors, including DNAM-1, TIGIT, and CD96, expressed on T and NK cells, which further transmit an alert signal to the immune system during malignant transformation. In fact, expression of CD155 was found to be correlated to the sensitivity of tumor cells towards NK cell-mediated cytotoxicity [16–18]. Additionally, it was reported that expression of CD155 mediated elimination of DNAM-1 dependent tumor cells by NK and CD8+ T cells. At the same time, CD155 expression, activated by DNA Damage Response pathway, stimulated NK cell-mediated elimination of malignant plasma cells [19]. Additional evidences demonstrated that CD155 expression inhibited anti-tumor activity of tumor cells in DNAM-1-deficient mice, and, over-expression of CD155 resulted in tumor rejection of/by NK cells, which was mediated by DNAM-1 [20,21]. However, during advanced clinical stages, CD155 might interact with inhibitory receptors to attenuate DNAM-1 mediated signals, when combined with upregulation of inhibitory receptors TIGIT and CD96 and decreased expression of DAMIN-1. This would further lead to inhibition of activation of NK and T cells, facilitating immune escape [22]. Remarkably, blockade of CD155 signaling has been previously shown to augment anti-tumor immunity [23]. All these studies indicated that CD155 played a critical in tumor progression; however, certain results were contradictory. A large number of studies have previously explored the clinical value of CD155, however, no previous study comprehensively analyzed CD155 expression and function in cancer patients.

METHODS

Search strategy: We conducted systematic retrieval through PUBMED, PMC, WEB OF SCIENCE, and other network databases

until May, 2022 and used the following retrieval formula "CD155" AND "cancer OR tumor OR neoplasm OR carcinoma" AND "prognosis OR Prognostic OR survival OR outcome", with the retrieval formula adjusted according to the format of different databases in the retrieval process.

Participant or population: Participants received a pathological diagnosis of cancer and received reasonable and effective therapeutic measures will be included.

Intervention: All participants were separated into cohorts, based on their CD155 levels, and survival analysis was completed on both cohorts.

Comparator: We will analyze clinico-pathologic and survival differences in cancer patients with different CD155 expressions.

Study designs to be included: Randomized controlled trials will be included.

Eligibility criteria: The pre-established inclusion criteria were as follows: (1) all subjects were cancer patients who received standard treatment; (2) The expression of CD155 in the cancer patients was well-examined, and all patients were assigned into two groups based on the expression; (3) survival analysis was performed based on these two groups, and provided sufficient data to estimate the risk ratio (HR) and 95% confidence interval (CI) for overall survival (OS); and (4) scientific and reasonable research. Case reports, reviews, abstracts, letters, bioinformatic analysis, TCGA analysis, and articles that did not meet the inclusion criteria were excluded from analyses.

Information sources: In the included literature, we collected the study data including authors, study region, sample size, cutoff scores, cancer type, and HR estimation, as well as the clinical data including age, gender, TNM stage, lymph node (LN) metastasis, distant metastasis, tumor size, and tumor grade.

Main outcome(s): The presented meta-analysis confirmed that over-expression of CD155 was associated with advanced tumor stage, positive of LN metastasis and distant metastasis, and worse OS. Therefore, it could be concluded that CD155 played a crucial role in cancer, and it could provide a strong/new direction for exploring/devising new strategies for cancer diagnosis and treatment.

Quality assessment / Risk of bias analysis: The Newcastle-Ottawa Quality Assessment Scale was applied to assess the quality of the included studies in this study. Begg's and Egger's tests were performed to analyze the publication bias.

Strategy of data synthesis: All statistical analyses were performed using the STATA 14.0 software, and two-sided $P < 0.05$ indicated statistical significance. The prognostic value of the included studies was assessed by HR. The collected HR and their corresponding 95% CI was integrated and pooled in SPSS software with established codes to estimate the association between CD155 expression and OS in cancer patients. Similarly, we evaluated the correlation between the CD155 expression and the clinical characteristics by pooling odds ratios (ORs) and their corresponding 95% CI. Notably, HRs derived from multivariate analysis were applied in all analysis, except for specifically designated grouping analyses. Consistent with other meta-analysis, we also used Chi-square test and I2 statistic to evaluate heterogeneity in SPSS software with established codes. However, irrespective of the results of Chi-square test and I2 statistics, the random models were used for all analyses for reducing the heterogeneity. We further explored the relationship between CD155 and the clinical characteristics and prognosis of cancer patients and the possible factors that contributed to heterogeneity through subgroup analyses. Moreover, the collected studies were grouped according to their publication date, detection method, sample size, analysis method, cut-off value, detected sample, and study region, and then Meta-

regression analysis was performed to find possible sources of heterogeneity.

Subgroup analysis: Subgroup analysis were performed according to cancer type, analysis method, publication date, detection method and study region.

Sensitivity analysis: Sensitivity analysis was performed to evaluate the stability of this study.

Language restriction: English.

Country(ies) involved: China.

Keywords: CD155; cancer; prognosis; biomarker; meta-analysis.

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