



The Prognostic Value of Natural Killer Cells and Their Receptors/Ligands in Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis

Jun-Shuai Xue¹, Zi-Niu Ding¹, Guang-Xiao Meng¹, Lun-Jie Yan¹, Hui Liu¹, Hai-Chao Li¹, Sheng-Yu Yao¹, Bao-Wen Tian¹, Zhao-Ru Dong¹, Zhi-Qiang Chen¹, Jian-Guo Hong¹, Dong-Xu Wang¹ and Tao Li^{1,2*}

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*Correspondence:

Tao Li
litao7706@163.com

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¹ Department of General Surgery, Qilu Hospital, Shandong University, Jinan, China, ² Department of Hepatobiliary Surgery, The Second Hospital of Shandong University, Jinan, China

Background: Natural killer (NK) cells play major roles in eliminating tumor cells. Preliminary studies have shown that NK cells and their receptors/ligands have prognostic value in malignant tumors. However, the relevance of NK cells and their receptors/ligands level to the prognosis of hepatocellular carcinoma (HCC) remains unclear.

Methods: Several electronic databases were searched from database inception to November 8, 2021. Random effects were introduced to this meta-analysis. The relevance of NK cells and their receptors/ligands level to the prognosis of HCC was evaluated using hazard ratios (HRs) with 95% confidence interval (95%CI).

Results: 26 studies were included in the analysis. The pooled results showed that high NK cells levels were associated with better overall survival (HR=0.70, 95%CI 0.57–0.86, P=0.001) and disease-free survival (HR=0.61, 95%CI 0.40–0.93, P=0.022) of HCC patients. In subgroup analysis for overall survival, CD57⁺ NK cells (HR=0.70, 95%CI 0.55–0.89, P=0.004) had better prognostic value over CD56⁺ NK cells (HR=0.69, 95%CI 0.38–1.25, P=0.224), and intratumor NK cells had better prognostic value (HR=0.71, 95%CI 0.55–0.90, P=0.005) over peripheral NK cells (HR=0.66, 95%CI 0.41–1.06, P=0.088). In addition, high level of NK cell inhibitory receptors predicted increased recurrence of HCC, while the prognostic role of NK cell activating receptors remained unclear.

Conclusion: NK cells and their inhibitory receptors have prognostic value for HCC. The prognostic role of NK cell activating receptors is unclear and more high-quality prospective studies are essential to evaluate the prognostic value of NK cells and their receptors/ligands for HCC.

Keywords: natural killer cells, receptor, ligand, hepatocellular carcinoma, prognosis

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common malignancy worldwide and the third leading cause of cancer-related mortality (1). The major risk factors for HCC involve chronic hepatitis B and hepatitis C infection, alcohol, and metabolic liver disease (2). Natural killer (NK) cells, characterized as CD3⁺CD56⁺ lymphocytes, are mainly involved in the early defense against virus infections and play major roles in eliminating tumor cells (3). NK cells account for only about 5–20% of the circulating lymphocytes in the peripheral blood. In contrast, NK cells are abundant in human liver, accounting for almost half of intrahepatic lymphocytes (4), which lays foundation for the powerful role of NK cells in the liver tumor microenvironment.

Human NK cells are divided into two major subpopulations based on the surface density of CD56 antigen (5). CD56^{dim} NK cells display a mature phenotype, accounting for approximately 90% of all NK cells and mediating the cytolytic response, while immature CD56^{bright} NK cells account for 5%–15% of total NK cells and are regarded as cytokine producers (6). Another surface marker is CD57, which is a marker for differentiated and highly cytotoxic NK cells, and is described as a phenotypically stable NK cells marker (7).

The regulation of NK cell function is mediated by a series of activated or inhibitory surface receptors. The major activated receptors involved in target cell killing are NK group 2 member D (NKG2D) and natural cytotoxic receptors (NCRs). NCRs mainly consist of NKp44, NKp46 and NKp30 (8), and can recognize ligands from different sources, including viral, parasitic, bacterial, as well as cellular ligands, such as HLA-B-associated transcript 3/Bcl-2-associated athanogene 6 (BAT3/BAG6), mixed lineage leukemia 5 (MLL5), proliferating cell nuclear antigen (PCNA) and B7 homolog 6 (B7-H6) (9, 10). In contrast, NKG2D mainly binds to the major histocompatibility complex class I chain-related protein A and B (MICA and MICB) and UL16-binding proteins (ULBPs). After binding, it can activate NK cells to produce cytotoxic substances to kill harmful and tumor cells (11). Other activated receptors include CD16, NKp88, CD244, CD226 and cytokine receptors such as interleukin (IL)-2R, IL-12R, IL-28R, IL-18R, IL-1R8, IL-15R, IL-10R, interferon receptor (IFNR) and tumor growth factor- β receptor (TGF- β R) (12–14).

The major inhibitory receptors involved in target cell killing are NKG2A, CD96, killer immunoglobulin-like receptors (KIRs), T cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain (TIGIT) and T cell immunoglobulin domain and mucin domain-3 (TIM-3) (12). Other inhibitory receptors include programmed cell death-1 (PD-1), lymphocyte activation gene-3 (LAG3), leukocyte-associated immunoglobulin-like receptors (LAIRs), adenosine 2A receptor (A2AR) and immunoglobulin-like transcripts (ILTs) (15). PD-1 is primarily expressed by activated T lymphocytes, but may also be expressed by NK cells in tumor patients. PD-1/Programmed cell death ligand-1 (PD-L1) interactions can inactivate T cells and NK cells, allowing tumor cells to escape immune surveillance (16). Human histocompatibility leucocyte antigen E (HLA-E) is the

main ligand of NKG2A, and is generally upregulated in cancer patients and predicts poor prognosis (17–19). The major histocompatibility complex class I (MHC-I) is the main ligand of KIRs, and is expressed on healthy hepatocytes. It interacts with inhibitory receptors on NK cells to prevent the activation of NK cells (14).

Until now, the correlation of NK cells and their receptors/ligands with the prognosis of HCC remains controversial (20–28). The purpose of this meta-analysis and review is to evaluate the prognostic value of NK cells and their receptors/ligands in HCC.

MATERIALS AND METHODS

Search Strategy and Study Selection Criteria

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (supplementary PRISMA Checklist) (29), and inclusion criteria were based on the PICOS model.

Relevant studies were independently searched by two authors (JSX, ZND) from the PubMed, Embase, Web of Science and Cochrane Library literature databases from the beginning of the database until November 8, 2021. Detailed search strategy was as described in the supplement. Additional articles were identified by a manual search of the references of eligible articles.

Studies were included if they met the following criteria. (1) all patients were identified as having HCC; (2) studies revealed the expression of NK cells and their receptors/ligands and obtained their levels by assaying; (3) studies provided adequate information to evaluate the hazard ratio (HR) and 95% confidence interval (95% CI); (4) the prognostic indexes such as overall survival (OS), cancer-specific survival (CSS), disease-free survival (DFS), recurrence-free survival (RFS), time-to-recurrence (TTR), and progression-free survival (PFS) were evaluated; (5) Anti-tumor treatments were not conducted; (6) studies must be published in English. Studies were excluded if they met the following criteria. (1) review, meta-analysis and case report; (2) basic experimental researches of HCC and studies unrelated to the NK cells and their receptors/ligands; (3) studies provided inadequate data to evaluate the correlation of NK cells and their receptors/ligands with prognosis. For republished studies, only the studies with the largest sample size were selected; alternatively, the most recent literature and relevant data were collected.

Data Extraction and Quality Assessment

Eligible study data were extracted independently by two investigators (JSX, ZND). Disagreements could be discussed and resolved with a third investigator (GXM). Baseline characteristics were extracted from the included studies. Only one study had outcome indicator for CSS, which we uniformly classified as OS. OS and DFS/RFS/TTR/PFS were used as

endpoints for the meta-analysis. The quality of eligible studies was assessed by the Newcastle–Ottawa Scale (NOS) criteria (30).

Statistical Analysis

Most of the relevant data from the studies could be directly collected. However, for those studies that did not provide hazard ratios (HRs) and 95% confidence intervals (95% CIs), we obtained estimates from known information using the method of Altman and Tierney (31, 32). Random effects models were applied. $P < 0.05$ was considered statistically significant. The pooled HR and 95% CI were used to assess the relevance between NK cell level and prognosis of HCC patients. Cochran's Q test and Higgins' I^2 statistic were used to assess the heterogeneity. P-value of heterogeneity > 0.10 and $I^2 < 50\%$ were considered as no significant heterogeneity. At the same time, subgroup analyses were performed by surface marker, source of NK cell, and outcome of patients. Sensitivity analysis was performed by removing each study to test the stability and reliability of the results. Funnel plots, Egger regression asymmetry tests, and Begg rank correlation tests were conducted to check for potential publication bias (33). Stata 16.0 software analysis was applied to all data in this meta-analysis.

RESULTS

Literature Search

As shown in **Figure 1** of the flowchart, a total of 1831 records were initially identified. After removing duplicate studies, 1110

studies were retained. After screening for titles and abstracts, 1052 studies were excluded. After reviewing the remaining 58 studies through full text, 32 studies were excluded due to insufficient data (11), public database (9), measurement of NKT (5), improper detection method including Ficoll separation or radiotaged NK-sensitive K-562 cell separation (2), and treatment of NK cells (5), including intravenous infusion of NK cells alone or combined with other modalities, such as radiofrequency ablation and irreversible electroporation. Finally, 26 studies were included in this analysis, including 13 on classical NK cells, 9 on activating receptors/ligands, 3 on inhibitory receptors/ligands, and 1 on both activating and inhibitory receptors/ligands.

The Basic Characteristics of Included Studies About NK Cells

Table 1 summarized the basic characteristics of the included studies about NK cells. Sample sizes of the eligible studies ranged from 36 to 258, for a total of 1711, and these studies were conducted primarily in two countries: twelve in China and one in Italy. Seven studies reported on CD56⁺ NK cells, 4 on CD57⁺ NK cells, and 2 on NK cells. Among these studies, 5 studies detected NK cells in peripheral blood, and 8 detected intratumor NK cells. In total, 12 studies mentioned the correlation between NK cell levels and OS (20–22, 25–27, 34–37, 39, 40). 9 studies mentioned the correlation between NK cells levels and DFS/RFS/TTR/PFS (20, 25–27, 35, 36, 38–40). NOS score > 6 was defined as high quality, and ≤ 6 was defined as low quality (**Supplementary Table 1**).

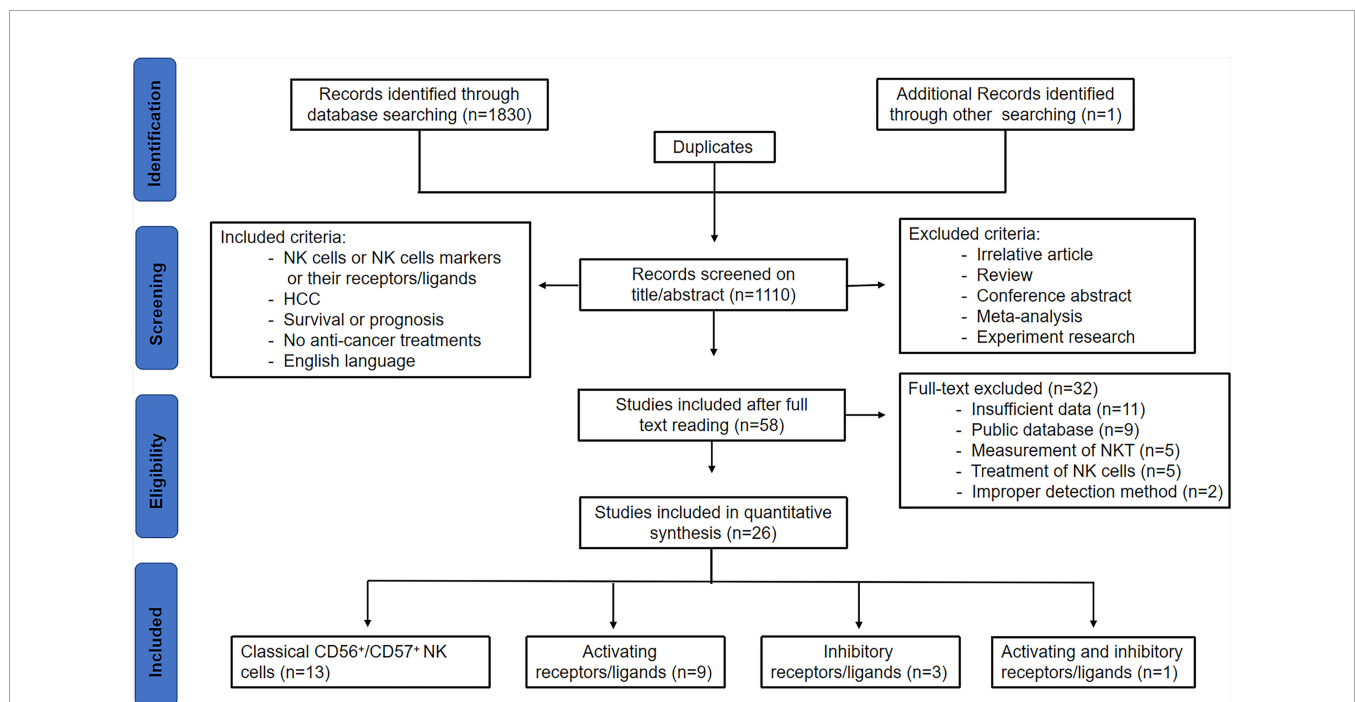


FIGURE 1 | Study flow chart of the data extraction process and selection of studies for meta-analysis.

TABLE 1 | The characteristics of all included eligible studies about NK cells.

Author	Year	Country	Sample size	Male/Female	Measurement	Marker	Treatment	Source	Tumor stage	VS	Number of VS	Divide	Outcome	Follow-up times	Score
Zhuang et al. (34)	2019	China	78	64/14	NA	CD56	mixed+SBRT	Peripheral blood	NA	High/Low	NA	cutoff value	OS;PFS	median:32 (4.1-80) month	7
Hu et al. (25)	2021	China	182	NA	Immuno histochemistry	resection	Intratumor	I-IV	High/Low	NA	NA	NA	OS;TTR	until 30/06/2016	7
Lin et al. (35)	2013	China	132	NA	Immuno histochemistry	resection	Intratumor	I-III	High/Low	NA	NA	cutoff value	OS;DFS	total:72 month	8
Wu et al. (20)	2013	China	256	115/15	Immuno histochemistry	resection/RFA	Intratumor	I-IV	High/Low	High/Low	126/130	median	OS;DFS	NA	9
Tao et al. (26)	2020	China	258	NA	Immuno histochemistry	resection	Intratumor	I-III	High/Low	High/Low	129/129	median	OS;TTR	NA	9
Chew et al. (22)	2012	China	36	NA	Immuno histochemistry	resection	Intratumor	I-IV	High/Low	High/Low	NA	median	OS	median:3.94 (0.9-5.5) year	6
Zhao et al. (21)	2014	China	163	131/32	Immuno histochemistry	resection	Intratumor	NA	High/Low	High/Low	82/81	median	OS	total:>60 month	9
Gao et al. (36)	2012	China	206	NA	Immuno histochemistry	resection	Intratumor	I-III	High/Low	High/Low	NA	median	CSS;RFS	median:48.1 (3.4-111.9) month	8
Cariani et al. (23)	2016	Italy	70	41/29	Flow cytometry	liver transplantation	Intratumor	NA	High/Low	High/Low	NA	median	OS;TTR	median OS:64 month; median TTR:16.5 month	7
Pan et al. (37)	2014	China	121	NA	Flow cytometry	resection+CIK	Peripheral blood	NA	High/Low	High/Low	NA	median	OS	until 31/12/2012	9
Liu et al. (38)	2021	China	100	NA	Immuno histochemistry	resection	Intratumor	NA	High/Low Positive/Negative	High/Low	60/61 31/68	median score	OS RFS	until 20/06/2020	6
Pan et al. (27)	2020	China	48	39/9	Flow cytometry	resection+CIK	Peripheral blood	NA	High/Low	High/Low	24/24	median	OS;RFS	total:>60 month	7
Che et al. (39)	2014	China	61	NA	Flow cytometry	resection	Peripheral blood	NA	High/Low	High/Low	33/28	median	OS;PFS	total:36 month	6

SBRT, Stereotactic body radiation therapy; RFA, Radiofrequency ablation; CIK, Cytokine-induced killer; Mixed, TACE or RFA or PEI or surgery or no treatment; TALE, Transcatheter arterial embolization; NK, Natural killer; OS, Overall survival; DFS, Disease-free survival; PFS, Progression-free survival; TTR, Time-to-recurrence; PFS, Progression-free survival; CSS, Cancer-specific survival. NA, Not available.

Prognostic Value of NK Cells in Patients With HCC

A total of 12 studies, involving 1611 patients, investigated the prognostic value of NK cells for OS. The pooled results from the 12 comparative studies were significant (HR=0.70, 95%CI 0.57-0.86, p=0.001), and the data were not heterogeneous (I² = 16.0%, P=0.287; **Figure 2A**). No bias was observed in the funnel plot (**Figure 3A**). In order to better understand the prognostic value of NK cells, we further performed subgroup analysis according to the marker and source of NK cells (**Table 2**). In subgroup analysis of CD57⁺ NK cells, the pooled results from 4 comparative studies were significant (HR=0.70, 0.55-0.89, P=0.004), while it was insignificant in CD56⁺ NK cells (HR=0.69, 95%CI 0.38-1.25, P=0.224; **Supplementary Figure 1**). Compared to peripheral NK cells (HR=0.66, 95%CI 0.41-1.06, P=0.088), the level of intratumor NK cells had better prognostic value (HR=0.71, 95%CI 0.55-0.90, P=0.005) for HCC patients (**Supplementary Figure 2**).

A total of 9 studies, involving 1313 patients, investigated the prognostic value of NK cells for DFS/RFS/TTR/PFS. The pooled results from the 9 comparative studies were not significant (HR=0.87, 95%CI 0.72-1.06, P=0.164), and the data were not heterogeneous (I² = 13.4%, P=0.323; **Figure 2B**). No bias was observed in the funnel plot (**Figure 3B**). We also performed subgroup analysis to better understand prognostic value of NK cells (**Table 2**). The pooled HR (95%CI) for CD57⁺ NK cells and CD56⁺ NK cells was 0.76 (0.57-1.01, P=0.059) and 1.09 (0.79-1.50, P=0.602), respectively (**Supplementary Figure 3**). For NK cells derived from peripheral blood and intratumor, the pooled HR (95% CI) was 0.93 (0.59-1.46, P=0.746) and 0.86 (0.68-1.09, P=0.213), respectively (**Supplementary Figure 4**). In addition, in subgroup analysis of outcome, we found that high NK cells levels could be a good predictor for DFS (HR=0.61, 95%CI 0.40-0.93, P=0.022), but not for RFS, TTR and PFS (**Supplementary Figure 5**).

Prognostic Value of Activating Receptors/Ligands on NK Cells

Table 3 summarized the outcomes of 3 studies that reported on NKp30⁺ NK cells. One study mentioned that high NKp30⁺ NK cell level was associated with better survival (41), while another study reported no effect of NKp30⁺ NK cell level on patient outcome (43). Other study suggested that high NKp30⁺ NK cell level was associated with good PFS, but not with OS (42). In addition, one study investigated the prognostic role of NKG2D. They concluded that low frequency of circulating NKG2D⁺CD56^{dim} NK cells one month after hepatectomy may predict a poor prognosis for patients with HBV-related HCC (23).

A total of 6 studies reported on ligands of NK cell activating receptors, including MICA, MICB, soluble MICA (sMICA), ULBP1 and B7-H6 (28, 44-48). The pooled HR (95%CI) for OS and DFS/RFS/PFS was 0.91 (0.52-1.57, P=0.726; **Figure 4A**) and 0.68 (0.26-1.75, P=0.422; **Figure 4B**), respectively.

Prognostic Value of Inhibitory Receptors/Ligands on NK Cells

Table 4 summarized the outcomes of 4 studies that mentioned NK cell inhibitory receptors, including NKG2A, CD96, CD158b,

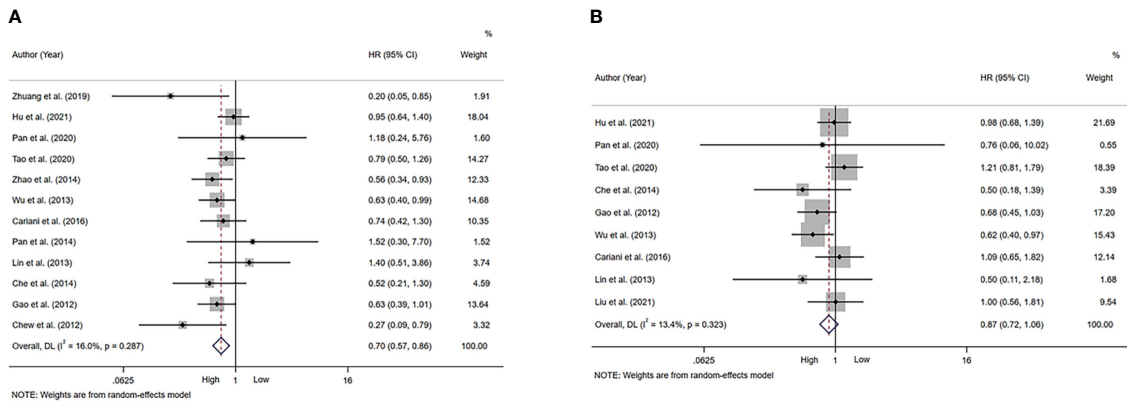


FIGURE 2 | Forest plot of NK cells in HCC. **(A)** Forest plot of NK cells and OS in HCC. **(B)** Forest plot of NK cells and DFS/RFS/TTR/PFS in HCC. CI, Confidence interval; HR, Hazard ratio; HCC, Hepatocellular carcinoma; NK, Natural killer; OS, Overall survival; DFS, Disease-free survival; RFS, Recurrence-free survival; TTR, Time-to recurrence; PFS, Progression-free survival.

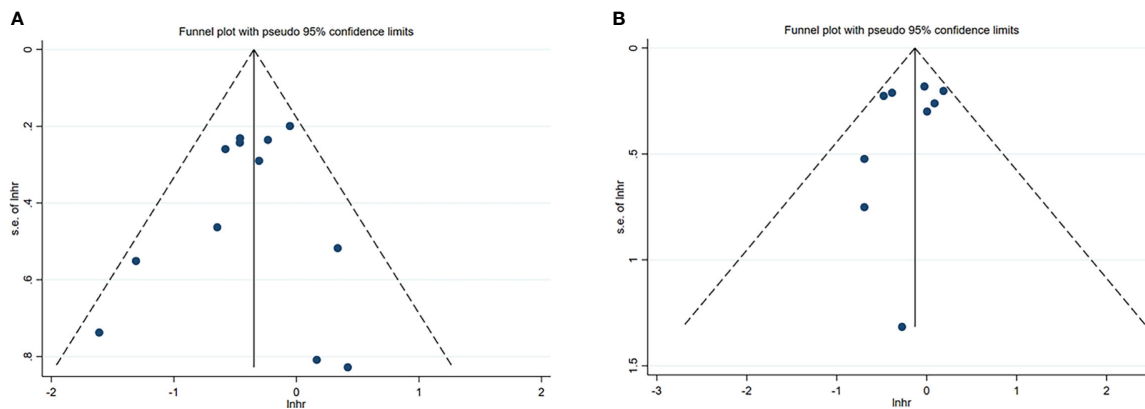


FIGURE 3 | Funnel plots of NK cells in HCC. **(A)** Funnel plots of HR for OS of NK cells. **(B)** Funnel plots of HR for DFS/RFS/TTR/PFS of NK cells. CI, Confidence interval; HR, Hazard ratio; HCC, Hepatocellular carcinoma; NK, Natural killer; OS, Overall survival; DFS, Disease-free survival; RFS, Recurrence-free survival; TTR, Time-to recurrence; PFS, Progression-free survival.

TIGIT and TIM-3 (24, 42, 49, 50). They all concluded that high level of NK cell inhibitory receptors predicted increased recurrence of HCC patients. Sun and Li et al. suggested that the level of NK cell inhibitory receptors was not associated with survival of HCC patients, while other studies revealed that high NK cell inhibitory receptors level predicted poor survival of HCC patients. One study found that intratumor level of HLA-E was increased, and high HLA-E level was correlated with poor prognosis of HCC patients (Figures 5A, B).

Assessment of Sensitivity Analysis and Publication Bias

Sensitivity analysis was performed to evaluate the stability of NK cells for predicting survival and recurrence of HCC patients. After removing any of the studies, the results did not exceed the

95% CI range of the pooled results (Figures 6A, B). Begg’s test and Egger’s linear regression test were used to assess whether there was potential publication bias in this meta-analysis. The results showed that no apparent publication bias for the analysis was found between NK cells and OS (Begg’s test: $P=0.732$, Figure 7A; Egger’s test: $P=0.564$, Figure 7B). Similarly, no significant publication bias was found for DFS/RFS/TTR/PFS analysis (Begg’s test: $P=0.602$, Figure 7C; Egger’s test: $P=0.401$, Figure 7D).

DISCUSSION

NK cells are innate lymphocytes that can kill virus-infected or cancer cells, and have a vital role in early hepatocarcinogenesis

TABLE 2 | Subgroup meta-analysis of the prognostic role of NK cells in HCC.

Factor	No. of study	No. of patients	HR (95%CI)	P-value	Heterogeneity	
					I ² (%)	P-value
OS						
Total	12	1611	0.70 (0.57-0.86)	0.001	16.0	0.287
Marker						
CD56	6	673	0.69 (0.38-1.25)	0.224	45.6	0.102
CD57	4	807	0.70 (0.55-0.89)	0.004	12.8	0.328
NK cells	2	131	0.67 (0.41-1.08)	0.103	0.0	0.532
Source						
Peripheral blood	5	378	0.66 (0.41-1.06)	0.088	12.0	0.337
Intratumor	7	1233	0.71 (0.55-0.90)	0.005	29.0	0.207
DFS/RFS/TTR/PFS						
Total	9	1313	0.87 (0.72-1.06)	0.164	13.4	0.323
Marker						
CD56	4	538	1.09 (0.79-1.50)	0.602	0.0	0.689
CD57	3	644	0.76 (0.57-1.01)	0.059	32.3	0.228
NK cells	2	131	0.84 (0.41-1.73)	0.641	43.8	0.182
Source						
Peripheral blood	3	179	0.93 (0.59-1.46)	0.746	0.0	0.406
Intratumor	6	1134	0.86 (0.68-1.09)	0.213	32.1	0.195
Outcome						
DFS	2	388	0.61 (0.40-0.93)	0.022	0.0	0.784
RFS	3	354	0.77 (0.55-1.08)	0.134	0.0	0.568
TTR	3	510	1.08 (0.85-1.36)	0.543	0.0	0.737
PFS	1	61	0.50 (0.18-1.39)	0.185	/	/

HCC, Hepatocellular carcinoma; NK, Natural killer; CI, Confidence interval; HR, Hazard ratio; OS, Overall survival; DFS, Disease-free survival; TTR, Time-to recurrence; RFS, Recurrence-free survival; PFS, Progression-free survival.

(51, 52). Different to T cells which require somatic gene rearrangement to produce highly antigen-specific receptors (53), NK cells are innately equipped with germline-encoded activating and inhibitory receptors that can directly determine whether NK cells are activated or inhibited (12, 54). NK cells can deliver cytotoxic granules, secrete effector cytokines, and are involved in death receptor induced apoptosis (55). NK cells can also rapidly produce cytokines with anti-tumor effects, such as IFN- γ , to exert their killing effects in the early stage of disease (56). In addition, NK cells can bind to target cells through surface CD16 and kill them through exerting antibody-dependent cell-mediated cytotoxicity (ADCC) (57). These results imply that NK cells play an essential role in the body's immune process in the defense against HCC.

In this study, we found that high NK cell level could predict better survival for patients with HCC. Similar results were previously reported in a meta-analysis of solid tumors (58). In subgroup analysis, CD57⁺ NK cells had better prognostic value over CD56⁺ NK cells. On the one hand, it may be that CD56⁺ NK cells, accounting for the majority of circulating NK cells, also expressed inhibitory molecules, which may strive for a dynamic balance between activating and inhibitory molecules. Moreover, lower IFN- γ production was also described in HCC, in accordance with the decreased cytotoxicity of NK cells (59). On the other hand, acquisition of CD57 represents a shift toward a higher cytotoxic capacity, greater responsiveness to signaling *via* CD16 and natural NCRs (60). The same result was also observed in Hu et al.'s

study (61). In addition, compared to peripheral NK cells, NK cells from intratumor had better prognostic value for prognosis of HCC patients, possibly because NK cells are abundant in human liver.

NK cells express activating and inhibitory receptors in order to perceive signals and display their activity. Depending on the received signal, NK cells can be activated or restricted (62). In this study, activating receptors/ligands mainly contain NKG2D, NKp30, and their ligands. NKG2D ligands mainly consist of ULBPs and MICA/B. MICA/B molecules expressed on HCC cells are recognized by NKG2D to induce ubiquitination-mediated endocytosis of the NKG2D-DAP10 complex, thereby activating NK cells to kill HCC (46, 57). NKp30 contains two ligands. One is BAT3, a nuclear protein that induces apoptosis in target cells by interacting with P53. The other is B7-H6, a newly discovered member of the B7 family that is expressed on the surface of tumor cells (45). B7-H6/NKp30 pathway is involved in the NK cell-mediated immune responses, and NK cells can recognize and eliminate B7-H6-expressing tumors, including HCC. However, tumors can also impair NK cell function by shedding B7-H6 membranes or decreasing NKp30 expression, leading to tumor immune escape and tumor progression (63). In addition, hypoxia, some soluble forms of NCRs ligands, or soluble factors produced by tumor/tumor-associated cells, can induce a decrease in both NCR expression and function (10, 64, 65), and protect tumor from NK cell-mediated cytotoxicity (44, 66). Until now, the prognostic value of activating receptors

TABLE 3 | The characteristics of included studies about the NK cells activating receptors and their ligands.

	Marker	Author	Year	Country	Sample size	Measurement	Treatment	Source	Tumor stage	VS	Number of VS	Divide	Outcome	P-value	Follow-up times
Activating receptors of the NK cells	NKp30	Chew et al. (41)	2010	Singapore	61	Immuno histochemistry	resection	Intratumor	I-III	High/Low	NA	median	OS	HR (95%CI) 0.34 (0.13,0.85) P=0.0144	median: 2.56 (0.02-9.11) year
	NKp30	Li et al. (42)	2021	China	25	Flow cytometry	untreated	Peripheral blood	NA	High/Low	16/9	cutoff value	OS;PFS	Log-rank test P=0.279; Log-rank test P=0.016	NA
	NKG2D	Gao et al. (23)	2016	China	20	Flow cytometry	resection	Peripheral blood	I-III	High/Low	10/10	median	OS;RFS	Log-rank test P=0.014; Log-rank test P=0.010	until:2014.11
Ligands of the NK cells activating receptors	NKp30	Rochigneux et al. (43)	2019	France	57	Flow cytometry	RFA	Peripheral blood	NA	High/Low	28/29	median	PFS	HR (95%CI) 0.61 (0.29,1.29) P=0.20	until:12/2016
	soluble MICA	Li et al. (44)	2013	China	60	ELISA	TACE	serum	III/IV	High/Low	28/32	median	OS	HR (95%CI) 1.47 (1.01,1.95) P<0.001	until:31/08/2010
	B7-H6	Qiu et al. (45)	2021	China	90	Immuno histochemistry	resection	Intratumor	I/II	High/Low	33/57	mean-H score	OS;DFS	HR (95%CI) 0.47 (0.24,0.93) P=0.029; HR (95%CI) 0.72 (0.36,1.43) P=0.1013	total:>60 month
	MICA	Zhang et al. (28)	2014	China	143	Immuno histochemistry	resection	Intratumor	I-IV	High/Low	NA	NA	OS;RFS	HR (95%CI) 0.91 (0.49,1.69) P=0.774; HR (95%CI) 1.43 (0.90,2.27) P=0.135	until:08/2013
	MICA/B	Fang et al. (46)	2014	China	96	Immuno histochemistry	resection	Intratumor	I-IV	High/Low	75/21	MICA/B expression score	OS	HR (95%CI) 0.32 (0.11,0.92) P<0.001	until:08/2012
	ULBP1	Kamimura et al. (47)	2012	Japan	54	Immuno histochemistry	untreated/resection	Intratumor	NA	Positive/Negative	25/47	expression	OS;RFS	HR (95%CI) 0.72 (0.09,5.70) P=0.120; HR (95%CI) 0.2 (0.06,0.65) P=0.006	NA
	ULBP1	Easom et al. (48)	2020	England	72	ELISA	untreated	serum	NA	High/Low	NA	NA	OS	HR (95%CI) 2.11 (1.02,4.02) P=0.0029	NA

NK, Natural killer; CI, Confidence interval; HR, Hazard ratio; RFA, Radiofrequency ablation; ELISA, Enzyme-linked immunosorbent assay; TACE, Transcatheter arterial chemoembolization; OS, Overall survival; DFS, Disease-free survival; RFS, Recurrence-free survival; PFS, Progression-free survival; NA, Not available.

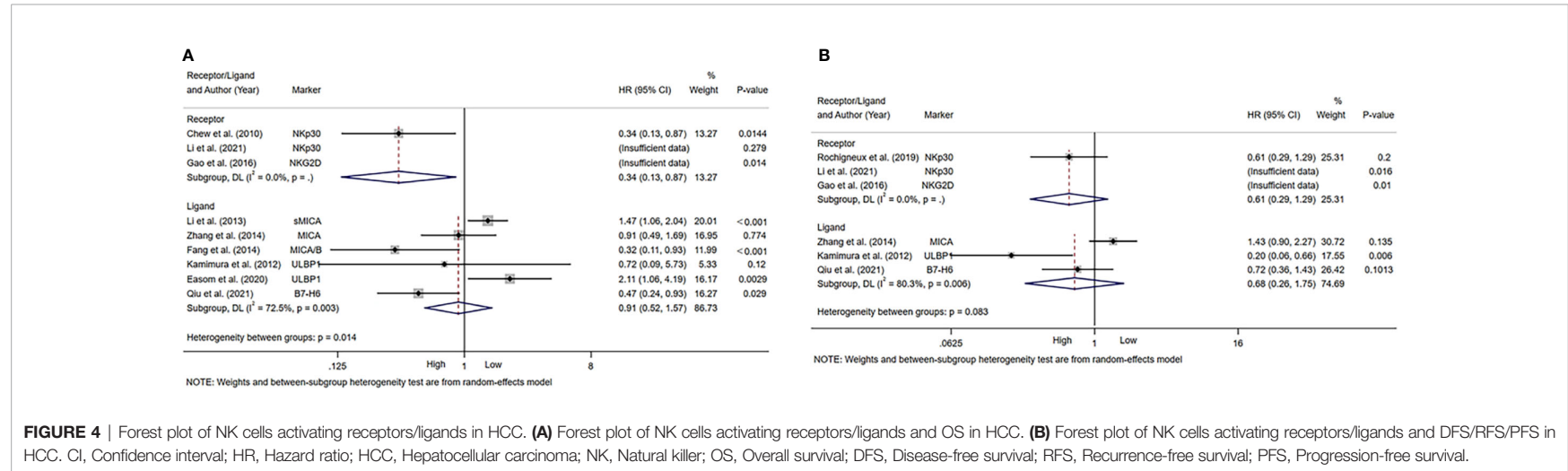


FIGURE 4 | Forest plot of NK cells activating receptors/ligands in HCC. **(A)** Forest plot of NK cells activating receptors/ligands and OS in HCC. **(B)** Forest plot of NK cells activating receptors/ligands and DFS/RFS/PFS in HCC. CI, Confidence interval; HR, Hazard ratio; HCC, Hepatocellular carcinoma; NK, Natural killer; OS, Overall survival; DFS, Disease-free survival; RFS, Recurrence-free survival; PFS, Progression-free survival.

TABLE 4 | The characteristics of included studies about the NK cells inhibitory receptors and their ligands.

Marker	Author	Year	Country	Sample size	Measurement	Treatment	Source	Tumor stage	VS	Number of VS	Divide	Outcome	P-value	Follow-up times
Inhibitory receptors of the NK cells	NKG2A	Sun et al. (24)	2017	China	177	Immune histochemistry	resection	Intratumor	NA	66/109	cutoff value	OS,DFS	HR (95%CI) 2.13 (1.28,3.56) P=0.0037; HR (95%CI) 1.93 (1.28,2.93) P=0.0018	median OS:1299.7 ± 1974.2 day; median DFS:980.0 ± 1796.1 day
	CD96	Sun et al. (49)	2019	China	236	Flow cytometry	resection	Intratumor	NA	NA	cutoff value	OS,DFS	Log-rank test P=0.5027; Log-rank test P=0.0484	NA
Ligands of the NK cells inhibitory receptors	CD158b	Li et al. (43)	2021	China	13	Flow cytometry	SBRT	Peripheral blood	High/Low	5/8	cutoff value	OS,PFS	Log-rank test P=0.273; Log-rank test P=0.003	NA
	TIGIT	Yu et al. (50)	2021	China	133	Flow cytometry	palliative/minimally invasive/resection	Peripheral blood	High/Low	65/68	cutoff value	PFS	HR (95%CI) 2.05 (1.24,3.04) P=0.005	NA
	TIM-3	Sun et al. (49)	2017	China	177	Immune histochemistry	resection	Intratumor	NA	High/Low	79/98	OS,DFS	HR (95%CI) 2.68 (1.58,4.56) P=0.0003; HR (95%CI) 2.41 (1.60,3.64) P<0.0001	median OS:1299.7 ± 1974.2 day; median DFS:980.0 ± 1796.1 day

NK, Natural killer; CI, Confidence interval; HR, Hazard ratio; SBRT, Stereotactic body radiation therapy; OS, Overall survival; DFS, Disease-free survival; PFS, Progression-free survival; NA, Not available.

remained inconsistent from different studies and deserved further investigation.

Inhibitory receptors/ligands mainly contain NKG2A, CD96, CD158b, TIGIT and TIM-3, and HLA-E. The NKG2A is expressed approximately in half of the peripheral blood NK cells, and is also expressed on CD8⁺ T cells (67). The inhibitory signals induced by NKG2A engagement can result in decreased capacity of NK cells and CD8⁺ T cells to lyse target cells (68), and enhanced expression of the HLA-E on tumor may result in resistance and immune escape by binding to NKG2A (68). Therefore, blocking the interaction of NKG2A with HLA-E has shown promising therapeutic effects in animal study (69). In addition, there is increasing evidence that PD-1 is also expressed on the surface of NK cells and exerts a suppressive function on T cell responses (16). In this study, though we found that inhibitory receptors of NK cells may be a good predictor for recurrence of HCC, however, their prognostic value in predicting survival was unclear. Therefore, more high-quality prospective studies are needed to explore the prognostic value of NK cells and their receptors/ligands for HCC.

The strength of this study is that it explored for the first time the prognostic value of NK cells and their receptors/ligands in HCC. Almost all relevant articles that could be collected were included and a comprehensive analysis was provided. However, the following limitations should also be considered. First, some of the data were not obtained directly from the included studies. HRs and 95% CIs were calculated using survival curves or 95% CIs were calculated from known P values and HRs, which may result in data inaccuracy to some extent. Second, although most studies used median as the cut-off value for NK cells level, these values were complex and related to the clinicopathological characteristics of the HCC patients. Third, although DFS/RFS/TTR/PFS of HCC patients are considered as composite outcome indicators, there are still slightly difference between them. Fourth, NK cells receptors/ligands are diverse. The pooled results may exist in bias to some extent. Fifth, this was an aggregate data rather than an individual data meta-analysis, and the data were various between studies, which somehow diminished the significance of the study. Finally, some surface markers were expressed not only in NK cells, but also in other immune cells, such as T cells, Dendritic cells (DCs), etc. Moreover, liver NK cells are composed of several subsets including conventional, type 1 innate lymphoid cells (ILC1) like, and liver-resident NK cells. All of them can express similar molecules and potentially be responsible for the clinical benefit observed (70).

CONCLUSIONS

In summary, we concluded that NK cells could be a good predictor for survival of HCC. More importantly, CD57⁺ NK cells may have better prognostic value over CD56⁺ NK cells, and intratumor NK cells have better prognostic value over peripheral NK cells. Inhibitory receptors of NK cell may be a good predictor for recurrence of HCC, but the value of activating

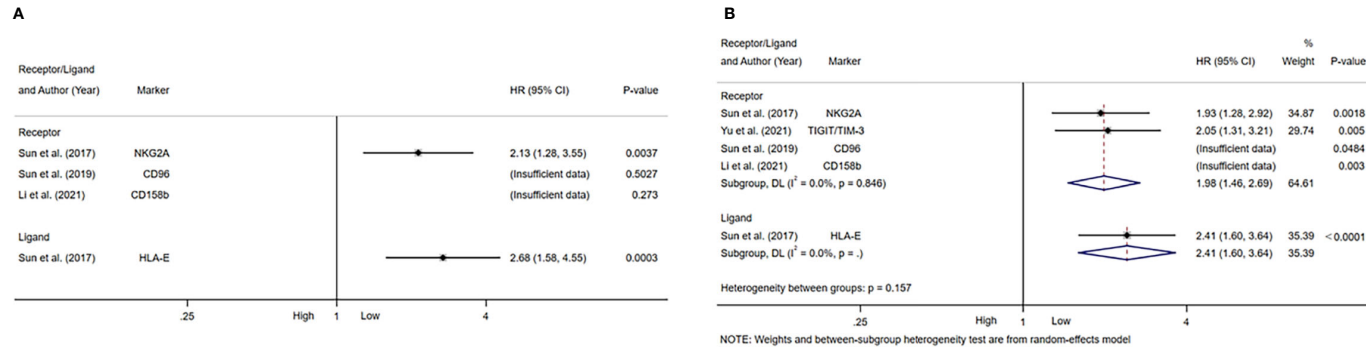


FIGURE 5 | Forest plot of NK cells inhibitory receptors/ligands in HCC. **(A)** Forest plot of NK cells inhibitory receptors/ligands and OS in HCC. **(B)** Forest plot of NK cells inhibitory receptors/ligands and DFS/PFS in HCC. CI, Confidence interval; HR, Hazard ratio; HCC, Hepatocellular carcinoma; NK, Natural killer; OS, Overall survival; DFS, Disease-free survival; PFS, Progression-free survival.

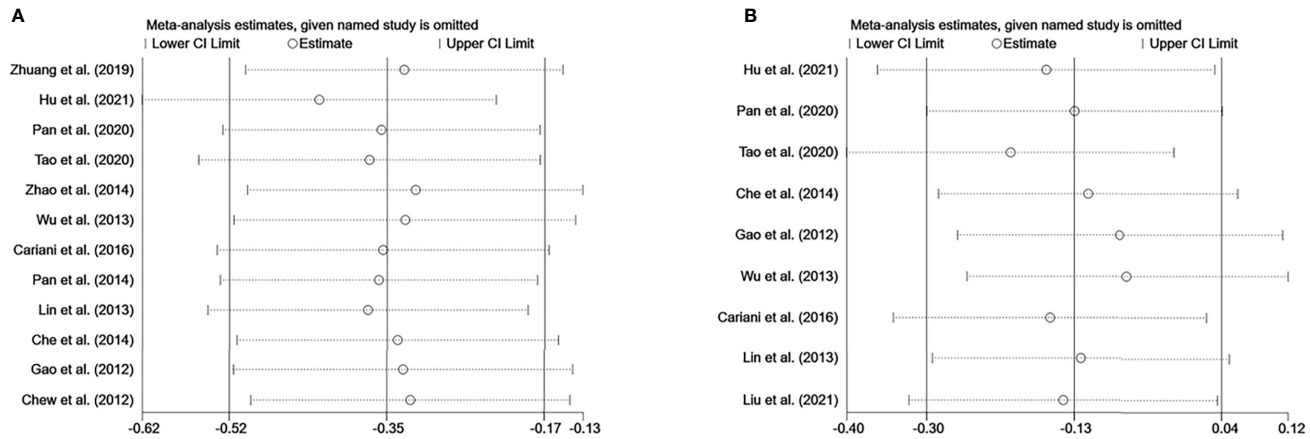
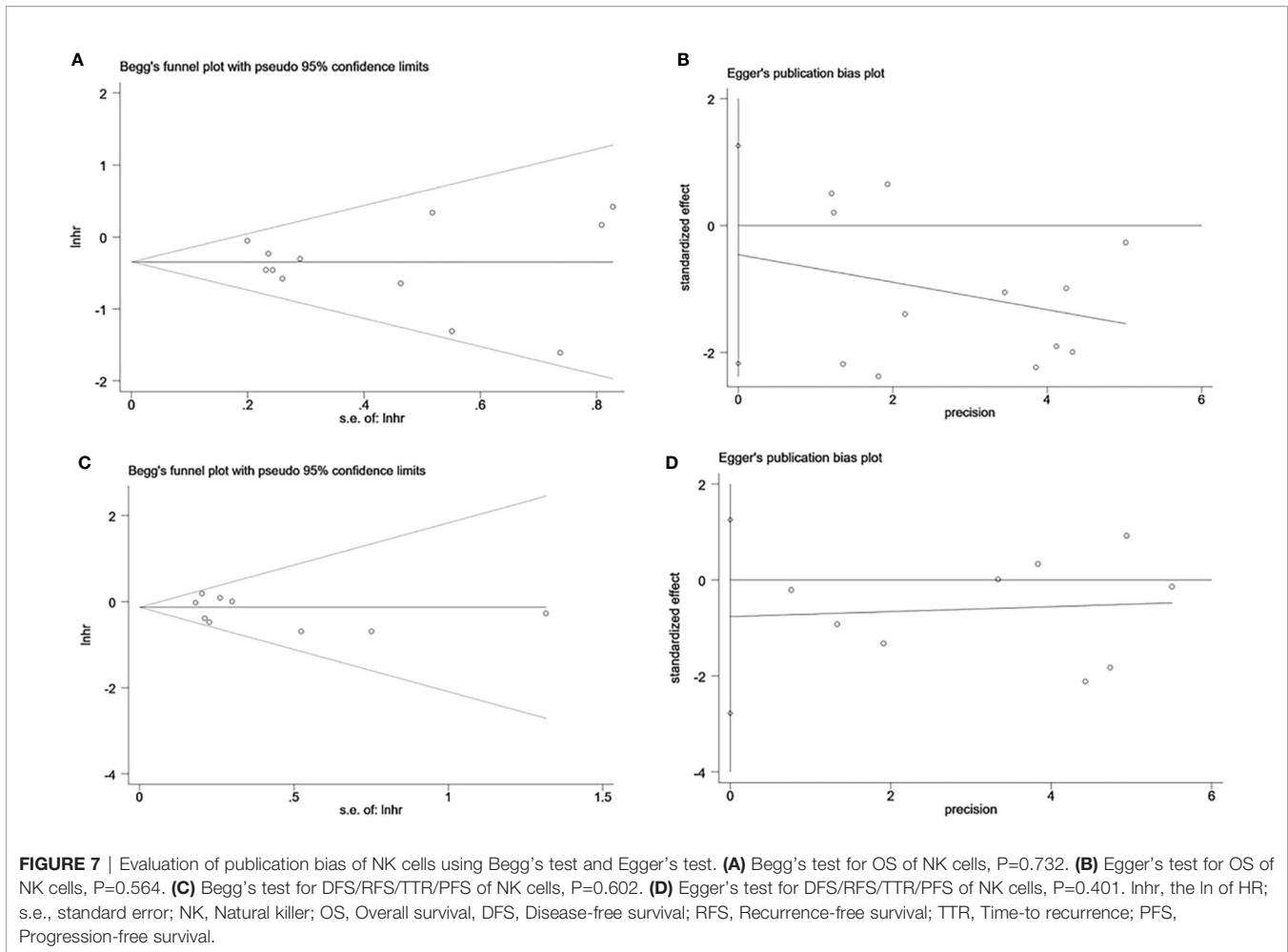


FIGURE 6 | Sensitivity analysis of NK cells. **(A)** Sensitivity analysis for OS of NK cells. **(B)** Sensitivity analysis for DFS/RFS/TTR/PFS of NK cells. CI, Confidence interval; HR, Hazard ratio; NK, Natural killer; OS, Overall survival; DFS, Disease-free survival; RFS, Recurrence-free survival; TTR, Time-to recurrence; PFS, Progression-free survival.



and inhibitory receptors in predicting the survival of HCC was unclear. More high-quality prospective studies are essential to evaluate the prognostic value of NK cells and their receptors/ligands for HCC.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

J-SX and TL were responsible for designing the study. J-SX, Z-ND, and G-XM conducted the systematic search and performed the screening. J-SX, Z-ND, G-XM, L-JY, HL, H-CL, S-YY, B-WT, J-GH, Z-RD, Z-QC, and D-XW primarily performed the quality assessment as well as supervision. J-SX analyzed, interpreted the data, and drafted the manuscript. TL

revised the manuscript. All data and material analyzed during this study were included in this article. All authors have read and approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fimmu.2022.872353/full#supplementary-material>

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GLOSSARY

NK	Natural killer
HCC	Hepatocellular carcinoma
HRs	Hazard ratios
CI	Confidence interval
NKG2D	NK group 2 member D
NCRs	Natural cytotoxic receptors
IL	Interleukin
IFNR	Interferon receptor
TGF- β R	Tumor growth factor- β receptor
BAT3	HLA-B-associated transcript 3
BAG6	Bcl-2-associated athanogene 6
MLL5	Mixed lineage leukemia 5
PCNA	Proliferating cell nuclear antigen
B7-H6	B7 homolog 6
MIC	Major histocompatibility complex class I chain-related protein
ULBPs	UL16-binding proteins
KIRs	Killer immunoglobulin-like receptors
TIM-3	T cell immunoglobulin domain and mucin domain-3
TIGIT	T cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain
PD-1	Programmed cell death-1
PD-L1	Programmed cell death ligand-1
LAG3	Lymphocyte activation gene-3
LAIRs	Leukocyte-associated immunoglobulin-like receptors
A2AR	Adenosine 2A receptor
ILTs	Immunoglobulin-like transcripts
HLA-E	Histocompatibility leucocyte antigen E
MHC-I	Major histocompatibility complex class I
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
OS	Overall survival
CSS	Cancer-specific survival
DFS	Disease-free survival
RFS	Recurrence-free survival
TTR	Time-to recurrence
PFS	Progression-free survival
NOS	Newcastle–Ottawa Scale
sMICA	Soluble MICA
ADCC	Antibody-dependent cell-mediated cytotoxicity
DCs	Dendritic cells
ILC1	Type 1 innate lymphoid cells
