The International Journal of Biological Markers
2020, Vol. 35(3) 3–13
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DOI: 10.1177/1724600820927409
journals.sagepub.com/home/jbm

The prognostic value of Immunoscore in patients with cancer: A pooled analysis of 10,328 patients

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Abstract
Objectives: Over the past decade, some publications have reported that Immunoscore was associated with the prognosis of several cancers. To better understand this issue, we conducted this pooled analysis.
Methods: We systematically searched PubMed, Embase, Web of Science, and the Cochrane Library from their inceptions to 15 May 2019 to identify relevant articles. The pooled hazard ratio (HR) and 95% confidence interval (CI) was estimated for overall survival, disease-free survival, and disease-specific survival.
Results: A total of 26 cohort studies with 10,328 patients involving eight cancer specialties were evaluated mainly by the consensus Immunoscore. The pooled analysis indicated that a lower Immunoscore was associated with a poor overall survival (HR 2.23, 95% CI 1.58, 2.70), disease-free survival (HR 2.40, 95% CI 1.96, 2.49), and disease-specific survival (HR 2.81, 95% CI 2.10, 3.77) for all cancers. The same convincing results were found in colorectal cancer, gastric cancer, and non-small cell lung cancer (especially the consensus Immunoscore for colon cancer). In five other types of cancer the results were similar, but the sample sizes were limited.
Conclusions: These findings support that Immunoscore is significantly associated with the prognosis of patients with cancer. It provides a reliable estimate of the risk of recurrence in patients with colon cancer. However, more high-quality studies are necessary to assess the prognostic value of Immunoscore in non-colon cancers.

Keywords
Immunoscore, cancer, prognosis, pooled analysis

Date received: 25 October 2019; revised: 6 March 2020; accepted: 22 April 2020

Introduction
The American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) tumor node metastasis (TNM) classification is the most common system to classify the extent of the spread of cancer. It has been a cornerstone of cancer care and research for decades and plays a critical role in cancer control, providing prognostic information and guiding individual treatment decisions. However, TNM does not meet all prognostic needs because of incomplete prognostic information. It has put the emphasis on tumor biology, while the prognosis is influenced by many factors such as age, sex, co-morbidity, performance status, host immune response, and so on. Patients with the same TNM stage have
had various clinical outcomes; a previous study showed that advanced stage patients can remain stable for years while TNM I/II-stage patients suffered from relapse, deterioration, and even rapid death. Tumor cells live in a complex microenvironment, which is closely connected with tumor growth and metastasis. Recently, an increasing number of studies have found that the adaptive immune system has a critical role in tumor development, which puts an emphasis on the importance of the systemic and local immunological biomarkers especially the tumor-infiltrating lymphocytes (TILs) in the prognosis of patients with cancer. In 1921, the immune cell infiltration of cancers was suspected to be a positive factor for patients with gastric cancer. Until 2018, there were more than 250 articles that investigated the association between the immune cell infiltrates of tumors and prognosis in 28 different cancers. Approximately 98% of studies found that the CD8+ T cell infiltration was associated with a good prognosis, and most studies were conducted on colorectal cancer. In order to investigate the influences of immune parameters on survival, Pagès et al. established the Immunoscore as a clinically prognostic marker, which based on the enumeration of two lymphocyte populations (CD3+/CD45RO+, CD3+/CD8+, or CD8+/CD45RO+) both in the center of tumor (CT) and the invasive margin (IM). Later, some studies found that the high Immunoscore was related to a better prognosis and it was validated by the international Immunoscore consortium, which involved 14 centers of 13 countries with 3539 TNM stage I–III colon cancer patients, in which the consensus Immunoscore was determined by the density of CD3+ and CD8+ T-cell in CT and IM. The conclusion was that the consensus Immunoscore could be used as a new component of a TNM-immune classification of colon cancer. Also, the Immunoscore can accurately predict the recurrence of colon cancer after 5 years of treatment, and can provide a more accurate prognosis compared with other parameters.

Over the past decade, some publications have reported that Immunoscore is associated with the prognosis of several cancers. However, few papers have evaluated the impact of Immunoscore on the prognosis of cancer patients. Although the paper by Sun et al. evaluated the prognostic value of Immunoscore in patients with colorectal cancer, the number of studies was limited and several of the latest studies were not included. Therefore, we systematically searched the existing publications and conducted a systematic review and meta-analysis to investigate the prognostic value of Immunoscore in all type cancers.

### Methods

#### Literature search

We systematically searched PubMed, Embase, Web of Science, and the Cochrane Library from the inception until 15 May 2019 to identify the articles that examined the prognostic value of Immunoscore in cancer patients. We used the following search strategy: (“cancer” OR “neoplasms” OR “carcinoma” OR “tumor” OR “adenocarcinoma” AND “Immunoscore” OR “immune score”). We also reviewed the references of related studies. We performed the meta-analysis under the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

#### Study selection

The inclusion criteria for the articles were those that: (a) illustrated the evaluation of Immunoscore; (b) showed overall survival (OS), disease-free survival (DFS) or disease-specific survival (DSS) in the endpoints; and (c) reported the hazard ratio (HR) estimates and related 95% confidence interval (CI) or survival curves. We excluded the reviews, commentaries, studies published only in abstract form, and studies that did not have sufficient primary data to calculate the HR.

#### Date extraction

The name of first author, year of publication, country, enrollment time, indicator, and geographic region of sampling, the number of participants, type and stage of cancer, duration of follow-up, outcomes, and their HR with 95% CI were extracted from each included study. If the study did not report the HR while the survival curves were available, we would calculate the HR by digitizing the curves using the open-source Engauge Digitizer software reported by Tierney et al.

#### Assessment of study quality

The Quality and Prognosis Studies (QUIPS) was used to assess the quality of included study, which was a valid and helpful tool for a systematic reviewer to critically assess the quality of study. The risk of bias was graded into three levels (including low, moderate and high) based on study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting.

#### Data synthesis and analysis

In this meta-analysis, we calculated the pooled HR and 95% CI to evaluate the prognostic value of the
Immunoscore for cancer patients. The $I^2$ and Cochran’s Q tests were used to evaluate the heterogeneity of each outcome. We also conducted the subgroup analyses by stratifying on the cancer site, clinical stage, follow-up duration, number of participants, indicators, and geographic region. Sensitivity analyses were conducted and publication bias was accessed. Review Manager 5.3 software (The Nordic Cochrane Centre, Copenhagen, Denmark) was used to conduct the systematic review and meta-analysis.

Results

Study selection and characteristics

In the literature search, we looked at 270 articles from the databases. Finally, 26 articles published between 2011 and 2019, were included for quantitative synthesis and meta-analysis. The processes of selection are shown in Figure 1.

Of these 26 cohort studies, a total of 10,328 (range 32–3539) cases were included from Europe, Asia, America, and Oceanic countries, which involved colorectal cancer ($n=16$), $^{8,19,22,24,25,27–31,35–38,40,41}$ gastric cancer ($n=2$), $^{23,39}$ non-small cell lung cancer (NSCLC) ($n=2$), $^{32,33}$ pancreatic cancer ($n=2$), $^{26,34}$ and one each in bladder cancer, $^{42}$ head and neck squamous cell carcinoma (HNSCC), $^{43}$ hepatocellular carcinoma (HCC), $^{21}$ and ovarian cancer. $^{20}$ The ranges of follow-up time were from 0 to 267 months. In the Mlecnik et al., $^{28}$ Nearchou et al., $^{30}$ and Jiang et al. studies, $^{39}$ more than one cohort was reported in each study, we recorded them one by one when analysis. The main characteristics of the 26 studies are shown in Table 1.

Survival outcomes in cancer patients

There were 20 studies with 8285 patients that reported the impact of Immunoscore on OS. The pooled HR was calculated with a random effects model because of the present heterogeneity among included studies. The statistical results showed that the lower Immunoscore was associated with a worse OS (HR 2.23, 95% CI 1.58, 2.70; $I^2 = 90\%$, $P_{\text{heterogeneity}} < 0.01$). Fifteen studies with 7288 patients provided the HRs and 95% CIs for DFS. The pooled results showed that a lower Immunoscore was associated with a worse DFS (HR 2.40, 95% CI 1.96, 2.49; $I^2 = 78\%$, $P_{\text{heterogeneity}} < 0.01$).

Nine studies with 3521 patients reported the outcomes of DSS. A lower Immunoscore was related to a poor DSS (HR 2.81, 95% CI 2.10, 3.77; $I^2 = 74\%$, $P_{\text{heterogeneity}} < 0.01$) (Figure 2 and Table 2).

We also conducted the subgroup analysis based on the consensus Immunoscore in which the scoring system is based on the density of CD3$^+$ and CD8$^+$ T-cell effectors in the CT and its IM. The results showed that lower Immunoscore was associated with poor OS (HR 2.12, 95% CI 1.60, 2.61; $I^2 = 93\%$, $P_{\text{heterogeneity}} < 0.01$), DFS (HR 2.22, 95% CI 1.70, 2.09; $I^2 = 71\%$, $P_{\text{heterogeneity}} < 0.01$) and DSS (HR 3.14, 95% CI 2.46, 4.02; $I^2 = 23\%$, $P_{\text{heterogeneity}} = 0.25$) for all included cancer (Table 3).

Survival outcomes in patients with colorectal cancer

Of 26 studies, 16 investigated the prognostic value of Immunoscore on patients with colorectal cancer (6703 patients). The statistical results showed that the lower Immunoscore were significantly associated with poor OS (HR 1.91, 95% CI 1.47, 2.49; $I^2 = 95\%$, $P_{\text{heterogeneity}} < 0.01$), DFS (HR 2.25, 95% CI 1.76, 2.87; $I^2 = 81\%$, $P_{\text{heterogeneity}} < 0.01$) and DSS (HR 3.07, 95% CI 2.13, 4.43; $I^2 = 74\%$, $P_{\text{heterogeneity}} < 0.01$) for patients with colorectal cancer.

More than 60% of the patients had colon cancer. Two studies with 4049 patients provided the HR and 95% CI in OS and DFS. $^{7,37}$ A lower consensus Immunoscore was significantly associated with poor OS (HR 1.85, 95% CI 1.47, 2.32; $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.58$) and DFS (HR 3.01, 95% CI 1.12, 8.55; $I^2 = 82\%$, $P_{\text{heterogeneity}} < 0.01$). The same result was found for DSS (HR 4.48, 95% CI 2.49, 8.05) in another study. In 2016, a study included 510 patients...
Table 1. The characteristics of included studies.

| First author          | Year  | Country       | Cancer Indicator | Region | Survival analysis | No. of patients | Year of recruitment | Stage | Age             | Follow-up period (month) |
|-----------------------|-------|---------------|------------------|--------|-------------------|-----------------|---------------------|-------|-----------------|--------------------------|
| Pagès et al.          | 2018  | 13 countries  | CD3+/CD8+        | CT/IM  | OS/DFS            | 3539            | 2013–2015           | I–III | 69 (60–77)      | 111 (105–116)            |
| Wirta et al.          | 2017  | Finland       | CD3+/CD8+        | CT/IM  | OS/DFS/DSS       | 510             | 2000–2010           | I–IV  | 73 (64–79)      | 72 (2.04–108)            |
| Mlecnik et al.        | 2018  | France        | CD3+/CD8+        | CT/IM  | OS/DFS           | 441             | 2004–2010           | IV    | NR              | NR                       |
| Park et al.           | 2017  | UK            | CD3+/CD8+        | CT/IM  | OS/DS            | 331             | 1997–2008           | I–III | 70 (55–85)      | 134 (108–170)            |
| Ko & Pyo              | 2019  | Korea         | CD3+/CD8+        | CT/IM  | OS                | 265             | 2001–2010           | I–IV  | NR              | 0 to 60                  |
| Wang et al.           | 2018  | China         | CD3+/CD8+        | CT/IM  | OS/DFS           | 249             | 2002–2015           | IV    | NR              | NR                       |
| Park et al.           | 2016  | UK            | CD3+/CD8+        | CT/IM  | DSS              | 246             | 1997–2008           | I–III | NR              | 150 (87–206)             |
| Van den Eynde et al.  | 2018  | Belgium       | CD3+/CD8+        | CT/IM  | DFS              | 222             | 2003–2009           | NR    | NR              | NR                       |
| Kwak et al.           | 2016  | Korea         | CD3+/CD8+        | CT/IM  | OS                | 196             | 2000–2010           | II    | NR              | 37.3 (0.8–104.6)         |
| Yomoda et al.         | 2019  | Japan         | CD3+/CD8+        | CT/IM  | OS/DFS           | 132             | 2009–2010           | II–III| NR              | NR                       |
| Antei et al.          | 2014  | France        | CD3+/CD8+        | CT/IM  | OS/DPS           | 111             | 1987–2004           | I–IV  | 74 (0–244)      | NR                       |
| Nearough et al.       | 2019  | Japan         | CD3+/CD8+        | CT/IM  | DSS              | 170             | 2002–2004           | II    | NR              | 138                      |
| Mlecnik et al.        | 2011  | France        | CD8+/CD45RO+     | CT/IM  | OS/DFS/DSS       | 599             | 1990–2004           | I–IV  | NR              | NR                       |
| Mlecnik et al.        | 2016  | France        | CD8+/CD45RO+     | CT/IM  | OS/DFS/DSS       | 270             | 2002–2003           | NR    | NR              | NR                       |
| Li et al.             | 2018  | China         | CD3+/CD8+        | CT/IM  | OS                | 60              | 2013–2016           | IV    | 59.6 ± 10.68    | 0 to 39                  |
| Ward-Harsthonge et al.| 2017  | New Zealand   | CD3+/CD8+        | CT/IM  | DFS              | 32              | 1995–2006           | II    | 72              | NR                       |
| Anitei et al.         | 2014  | France        | CD3+/CD8+        | CT/IM  | OS                | 132             | 2009–2010           | II–III| NR              | NR                       |
| Zhang et al.          | 2018  | China         | CD3+/CD8+/CD45RO+| CT/IM  | OS/DFS/DSS       | 879             | 2005–2009           | I–IV  | NR              | NR                       |
| Kim et al.            | 2017  | Korea         | CD3+/CD8+        | CT/IM  | EC/SC            | 153             | 2004–2009           | NR    | NR              | NR                       |
| Paulsen et al.        | 2015  | Norway        | CD8+/CD45RO+     | CT/IM  | DSS              | 536             | 1990–2010           | I–III | 67 (28–85)      | 86 (34–267)              |
| Paulsen et al.        | 2017  | Norway        | PD-1/PD-LI       | EC/SC  | DSS              | 633             | 1990–2010           | I–III | 67 (28–85)      | 86 (34–267)              |
| Yu et al.             | 2018  | Canada        | CD3+/CD8+        | CT/IM  | OS/DFS           | 67              | 2011–2013           | pT1–pT4| 68.9 (17.5)*    | 21.9 (15.3–32.5)         |
| Yao et al.            | 2017  | China         | CD8+/CD45RO+     | CT/IM  | DSS              | 92              | 2006–2011           | I–IV  | 46.7 (22–77)    | NR                       |
| Zhang et al.          | 2018  | China         | HNSCC            | CT/IM  | OS/DFS           | 88              | 2009–2015           | I–III | 36              | NR                       |
| Bosmuller et al.      | 2016  | Germany       | CD3+/CD103+      | IC/SC  | OS                | 138             | 2000–2008           | II–IV | 35–85           | 1 to 120                 |
| Tahkola et al.        | 2018  | Finland       | CD3+/CD8+        | CT/IM  | OS/DFS           | 108             | 2000–2016           | I–II  | 66.9 (8.2)*     | 44 (15.8–57.3)           |
| Miksch et al.         | 2019  | Germany       | CD3+/CD8+        | CT/IM  | OS/DFS           | 57              | NR                 | NR    | 70.4            | 19                       |

BC: bladder cancer; CC1: colon cancer; CC2: cellular components; CRC: colorectal cancer; CT: core/center of tumor; DFS: disease-free survival; DSS: disease-specific survival; EC: epithelial compartments; GC: gastric cancer; HCC: hepatocellular carcinoma; HNSCC: head and neck squamous cell carcinoma; IC: intraepithelial compartment; IM: invasive margin; NR: not reported; NSCLC: non-small cell lung cancer; OC: ovarian cancer; OS: overall survival; PC: pancreatic cancer; PD-1: programmed death-1 receptor; PD-L1: programmed cell death-ligand 1; RC: rectal cancer; SC: stromal components.

*interquartile range

#standard deviation
A higher Immunoscore was related to improved OS, DFS, and DSS. According to the multivariable analysis with the Cox proportional hazard model, the HR of the lowest Immunoscore was 2.47 (95% CI 1.66, 3.67) for OS, 5.68 (95% CI 2.42, 23.31) for DFS, and 4.48 (95% CI 2.49, 8.05) for DSS compared with the highest Immunoscore. Recently, similar results were found in 3539 patients with stage I–III colon cancer from a 14-center (13 countries) study published in *The Lancet*, which showed that patients with a high Immunoscore had a lower risk of recurrence at 5 years (rate of recurrence 8%), while higher risk of recurrence in patients with a low Immunoscore (rate of recurrence 32%).

We also conducted a subgroup analysis by stratifying the cancer site, the clinical stage of tumor, the follow-up duration, the number of participants, the indicators, and the geographic region. Similarly, a lower Immunoscore was associated with a bad

### Table 2. Results based on cancer type

| Cancer | study | OS | DFS | DSS | P |
|--------|-------|----|-----|-----|---|
| CRC    | 2016  | 895  | 1020 | 928  | <0.001 |
| HCC    | 2012  | 32   | 239  | 236  | 0.43 |
| NSCLC  | 2010  | 22   | 256  | 226  | 0.23 |
| BCC    | 2014  | 137  | 167  | 165  | 0.14 |
| OC     | 2016  | 585  | 699  | 691  | 0.003 |
| BC     | 2016  | 198  | 230  | 220  | 0.46 |

BC: bladder cancer; CRC: colorectal cancer; OS: overall survival; DFS: disease-specific survival; NSCLC: non-small cell lung cancer; HCC: hepatocellular carcinoma; HNSCC: head and neck squamous cell carcinoma; HR: hazard ratio; NS: not significant; OC: ovarian cancer; PC: pancreatic cancer.
prognosis despite the cancer site (colorectal, colon, rectal), the number of participants (>300 or <300), the stage of tumor (I–III or IV) or the maximum follow-up time (>10 years or <10 years). However, there was no significant difference in DFS for Asian patients (Table S1).

Survival outcomes in patients with gastric cancer

Two studies with 1032 patients identified the influence of Immunoscore for gastric cancer prognosis based on the OS and DFS. The polled HRs were calculated with a fixed-effects model because there was no heterogeneity. Lower Immunoscore was associated with worse OS (HR 2.78, 95% CI 2.31, 3.35; $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.82$) and DFS (HR 2.81, 95% CI 2.33, 3.38; $I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.63$) (Table 2).

Two studies investigated the connection between Immunoscore and prognosis of gastric cancer patients. The Jiang et al. study with 879 patients represented that a higher Immunoscore had a significant survival advantage in OS and the Immunoscore was calculated by a specific formula, which depended on the density of CD3, CD8, CD45RO, and CD66b from CT and IM. In another study, the Immunoscore system was calculated based on the density of the CD3$^+$ and CD8$^+$ TILs from both epithelial and stromal compartments of the CT and the IM. However, the results were similar with Jiang et al. study.

Survival outcomes in patients with NSCLC

Two studies with 1169 patients provided the HRs and 95% CI for DSS. The polled results showed that lower Immunoscore was related to poor DSS (HR 1.81, 95% CI 1.12, 2.92; $I^2 = 63\%$, $P_{\text{heterogeneity}} = 0.1$) (Table 2). Paulsen et al. conducted two studies that included 536 patients with TNM stage I–IIIA to access the prognostic value of Immunoscore for NSCLC. The Immunoscore was based on CD8+/CD45RO+ TILs in one study and PD-1/PD-L1 in the other study.

Survival outcomes in other cancer patients

Regarding HCC, HNSCC, pancreatic, bladder and ovarian cancer, the lower Immunoscore was associated with a worse prognosis compared with the higher Immunoscore. The results were similar even though the sample sizes of all studies included were limited. The statistical results are shown in Table 2.

Sensitivity analyses

In order to eliminate the over-dependence of the results on an individual study, we conducted the sensitivity analyses for OS, DFS, and DSS based on the weights in all studies. There were no significant differences
influenced by removing any one study that was most weighted.

**Quality assessment**

According to the QUIPS criteria, about 46.2% articles had a low risk of bias. More than half of the 26 articles had a moderate-to-high risk of bias. Detailed information regarding quality assessment is shown in Table S2.

**Publication bias**

For the studies included in the OS, DFS, and DSS analyses, the funnel plots suggested evidence of publication bias (Figure S1).

**Discussion**

The immune system plays a critical role in tumor development. The protective value of immunity was initially proposed by Paul Ehrlich in 1909; however, it was impossible to access the validity of the prediction because of the limited awareness of the composition and function of the immune system. In the 2000s, mouse studies confirmed that the immune system was an effective tumor-suppressor system and affected the development and progression of cancer in which immunodeﬁcient mice developed tumors earlier and with greater frequency compared with the wild-type mice in the same condition. Later, similar results were conﬁrmed in human colorectal cancer.

In 2005, Pagès et al. investigated the role of tumor-inﬁltrating immune cells in the early metastatic invasion of colorectal cancer and demonstrated that patients with a high density of inﬁltrating memory and effector memory T cells (CD45RO+) were less likely to disseminate to lymphovascular and perineural structures and to regional lymph nodes. Subsequently, they characterized the tumor-inﬁltrating immune cells in large cohorts of human colorectal cancers by gene expression proﬁling and in situ immunohistochemical staining. They found that the immunological data (the type, density, and location of immune cells within the tumor samples) seemed to be a better predictor of patient survival than the histopathological methods. In the study, the patients without recurrence had higher densities of CD3+, CD8+, and CD45RO+ immune cells than those patients with recurrent tumors and had a longer survival. For the tumor location, they found that combining the two regions of CT and IM could improve the prediction of patient survival. CD3+CT/CD3+IM density especially was the only independent parameter associated with OS and DFS according to multivariate analysis. The theory was that immune cells would release the cytotoxic mediators when stimulated by an antigen to destroy and kill the tumor cells, which was called “adaptive immune response.” For example, CD3+CD8+ T cells with cytotoxic granules that contain perforin and granzymes, which were released on interaction with target cells expressing cognate antigen, led to the death of target cells by apoptosis.

In the following years, Galon and colleagues created the concept of “Immunoscore,” which was used to reflect the prevalence of immune inﬁltrates in tumor microenvironment and was determined by the density, location, and type of different immune inﬁltrate-cells such as total T cells (CD3+), cytotoxic T cells (CD8+), memory T cells (CD45RO+), and the scoring system ranged from Immunoscore 0(10)—which had low densities of both cell types in both regions—to Immunoscore 4(14), having high densities of both cell populations in both locations. In order to standardize the measurement of immune inﬁltrates and promote the utilization of Immunoscore in clinical practice internationally, a working group composed of the Society for Immunotherapy of Cancer (SITC), the Europe Academy of Tumor Immunology (EATI) and “La fondazione Melanoma Onlus” was formed to validate the consensus Immunoscore in clinical practice for patients with stage I–III colon cancer, which was defined as the density of CD3+ and CD8+ T-cell effectors both in CT and IM because the CD3 and CD8 were the two easiest membrane stains. The results were recently reported by Pagès et al. that Immunoscore provided a reliable estimate of the risk of recurrence in patients with colon cancer and the implementation of the consensus Immunoscore as a new component of a TNM-Immune classiﬁcation of cancer. In this meta-analysis, approximately 87.5% studies were in line with the consensus Immunoscore in terms of the measurement of immune inﬁltrates.

Many studies showed that the prognosis value of Immunoscore was superior to microsatellite-instability (MSI) staging. Pagès et al. analyzed the connection of the Immunoscore and MSI status in 1579 patients with colon cancer and found that patients with high Immunoscore had prolonged OS, DFS, and time to recurrence no matter what their MSI status was. In a multivariate Cox model, Immunoscore was a signiﬁcant predictor for OS, DFS, and time to recurrence, while MSI remained a signiﬁcant factor for time-to-reurrence but not for OS and DFS. Similar results were found in other studies.

All the evidence has proved that Immunoscore could be used as a prognostic biomarker that can be standardized across pathology laboratories especially for colon cancer. Also, it can be used as an actionable predictive biomarker of responsiveness to both chemotherapy and immunotherapy, which has been recently under investigation. Finally, the Immunoscore...
In gastric cancer, the immune infiltration cells have been investigated since the early 1900s. Increasing evidence has indicated the association between immune infiltration and clinical outcomes. However, there was no consensus in the measurement of Immunoscore. In our meta-analysis, the Immunoscores of NSCLC were based on epithelial CD45RO+/stromal CD8+ and PD-1/PD-L1 respectively. The uniform measurement of Immunoscore is also needed for NSCLC.

Recently, the value of Immunoscore has been investigated in several other types of cancer, including ovarian cancer, hepatocellular carcinoma, pancreatic cancer, bladder cancer, head and neck squamous cell carcinoma. However, the number of studies in the literature is limited (see Table 1 and Table 2). Bösmüller et al. found that the combined assessment of CD103 and CD3 counts improves the prognostic value of TIL counts in high-grade serous ovarian cancer. In this paper, patients with CD3high/C103high tumors showed a 5-year survival rate at 90%, CD3low/CD103high at 63%, and CD3low/CD103low at 0% ($P < 0.001$). Yao QW investigated the value of IS staging system in hepatitis B virus-related hepatocellular carcinoma (HBV-HCC), and found IS was correlated significantly with OS. They suggested the IS staging was closely related to the outcome of patients, and it can compensate the TNM tumor classification system in predicting the prognosis of HBV-HCC patients. Similar results were found for patients with bladder cancer or head and neck squamous cell carcinoma. Given the limited number of studies, further research is needed.

In this meta-analysis and systematic review, we searched existing publications to summarize the evidence of the prognostic value of Immunoscore in all types of cancer, and found that Immunoscore is significantly associated with the prognosis of patients with cancer. The pooled results indicated that a lower Immunoscore was associated with a poor OS, DFS, and DSS for all cancers. Also, we conducted a subgroup analysis stratified by cancer sites, clinical stage, period of follow-up, number of participants, indicator, and geographic region for patients with colorectal cancer. The results were similar except for the geographic region, which showed that low Immunoscore was significantly correlated with poor prognosis for Europeans, but not significantly correlated with Asians. The results indicated that there may be racial differences in the impact of Immunoscore on the prognosis of colorectal cancer. Considering the number of studies based on Asian populations is limited, future studies are needed to investigate the difference in survival between different races. In addition, in five other studies are needed to investigate the difference in survival between different races. In addition, in five other
types of cancers, the results were similar, but the sample sizes were limited, and there were different indicators for individual cancers.\textsuperscript{26,34} Therefore, more studies are warranted to identify the more valuable and reasonable indicators for those cancers.

We systematically evaluated the prognostic role of Immunoscore in eight types of cancer with a large sample size. However, there were several limitations. First, heterogeneity was found between the included studies. The reasons were the different immune cells, various measurements of Immunoscore, and the different cancer types; heterogeneity may also be caused by different follow-up times in each study. We conducted the subgroup analysis and the sensitivity analysis to reduce the high heterogeneity. Second, there were not enough studies in some cancer specialties—especially ovarian cancer, bladder cancer, and HNSCC. Third, the impact of Immunoscore was different between different cancer sites and clinical stages, but we did not perform a subgroup analysis in other cancers (except the colorectal cancer) because of the limited sample size, and the primary information about the each patient was unavailable. Fourth, the scoring cutoffs were different among studies. Finally, publication bias would have had an impact on the results.

Conclusion

Immunoscore had a prognostic value in predicting the progression for all kinds of cancers included in the study, which can be used as a supplementation of TNM classification especially for colorectal cancer. The consensus Immunoscore could be used as a new component in classification for colon cancer. Also, it is possible to use Immunoscore to predict recurrence and to guide adjuvant treatment allocation for patients with colon cancer. However, more high-quality studies are needed to investigate the association between Immunoscore and prognosis for other types of cancer.

Declaration of conflicting interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by Chinese Medical Board Grant on Evidence-Based Medicine, New York, USA (No. 98-680), National Natural Science Foundation of China (No.30901427) and Sichuan Provincial Science and Technology Support Project (2016SZ0047) and National Natural Science Foundation of China (No.71974135).

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Supplementary material:

Supplemental material for this article is available online.

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