Review

Clinical Cancer Research

Prognostic Significance of Tumor-Infiltrating B Cells and Plasma Cells in Human Cancer

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Abstract

There is abundant evidence that tumor-infiltrating $CD8^+$ T cells contribute positively to antitumor immunity; however, the role of tumor-infiltrating B cells (TIL-B) and plasma cells (PC) remains controversial, leading to differing opinions about whether immunotherapies should be designed to enhance or inhibit these cells. Through a comprehensive PubMed search, we reviewed publications with cohorts of 50 or more cases in which the prognostic value of TIL-B/PC was assessed by immunohistochemistry and/or gene-expression analysis. Sixty-nine studies representing 19 cancers met our review criteria. The large majority of studies assessed TIL-B by immunohistochemical detection of CD20. Of these, 50.0% reported a positive prognostic effect for $CD20^+$ TIL-B, whereas the remainder found a neutral (40.7%) or negative (9.3%) effect. These differences in prognostic effect were not attributable to cancer type, other clinicopathologic factors, or differing technical approaches. The prognostic significance of TIL-B/PC was generally concordant with that of $CD3^+$ and/or $CD8^+$ T cells, and the prognostic effect of T cells was generally stronger when TIL-B and/or PC were also present. Additionally, 21 studies inferred the presence of TIL-B/PC from gene-expression data, and a large majority reported a positive prognostic effect. Although more studies are required involving additional cancer types and independent patient cohorts, the weight of evidence supports a positive role for TIL-B and PC in antitumor immunity, suggesting that enhancement of these responses should be considered in the design of cancer immunotherapies. *Clin Cancer Res; 24(24); 6125–35. ©2018 AACR.*

Introduction

Although the prognostic significance of tumor-infiltrating T cells has been broadly accepted (1), there remains considerable controversy over the influence of tumor-infiltrating B lymphocytes (TIL-B) and plasma cells (PC). By a strict interpretation of the Th1/Th2 paradigm, Th1/cytolytic and Th2/humoral immune responses are mutually exclusive in that the conditions favoring one are inhibitory toward the other. From this, one might conclude that strategies to inhibit Th2/humoral responses might promote stronger Th1/cytolytic responses against cancer. On the other hand, coordinated antibody and T-cell responses to tumor antigens such as NY-ESO-1 are well documented in cancer (2, 3), revealing that the Th1/Th2 paradigm is not absolute. Moreover, cancer immunotherapies such as vaccines and checkpoint blockade enhance both T-cell and B-cell responses (4, 5), which is typically viewed as a desirable outcome. Furthermore, in autoimmunity and allograft rejection, cooperation between B cells and T cells is well established and indeed associated with the most aggressive immune responses against tissues (6, 7). For this reason, B-cell depletion has become a therapeutic approach for autoimmune conditions such as multiple sclerosis, lupus, and rheumatoid arthritis (8–10). Thus, to develop more effective immunotherapies for human cancer, it is critical to understand the role of B cells and PC in antitumor immunity.

Toward this goal, we report here the results of a systematic review of publications addressing the prognostic significance of TIL-B and PC in human cancer. Our findings support a positive role for TIL-B and PC in antitumor immunity and provide guidance for the design of future studies to further clarify this issue.

Search strategy

We searched PubMed for peer-reviewed articles reporting on the prognostic effect of TIL-B and/or PC in any human cancer except leukemia, lymphoma, myeloma, and lymphoproliferative disease due to the obvious confounding issues. We searched for studies involving any member of the B lineage, including naïve B cells, activated/memory B cells, plasmablasts, and PC. The following search terms and logic gates were used for the PubMed search: "B-cell" AND "cancer" AND "prognosis" NOT "(lymphoma myeloma leukemia lymphoproliferative)." For articles on PC, the search terms were modified to "plasma cell" AND "cancer" AND "prognosis" NOT "(myeloma lymphoma lymphoproliferative `cell-free' amyloid leukemia amyloidosis myofibroblastic pseudotumor plasmacytoma)." Furthermore, we reviewed citations in selected papers and "related articles" suggested by PubMed to identify additional relevant articles.

We focused on studies that used (i) immunohistochemistry (IHC) to detect TIL-B and PC in solid tumors and/or (ii) gene-expression signatures that are unique to or closely related to the

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B-cell lineage. As an inclusion criterion, studies had to report the standard prognostic endpoints of overall survival (OS), disease-specific survival (DSS), and/or progression-free survival (PFS); studies that instead used parameters such as tumor stage or response to therapy were excluded. The search was limited to publications in the English language. To maintain a reasonable standard of statistical rigor, we excluded studies with sample sizes below 50. The search encompassed articles listed in PubMed on or before December 1, 2017.

Data elements

We attempted to retrieve the following data from all publications: tumor type, stage, grade, primary or chemotherapy-pretreated samples, number of study subjects, method of analysis, type of survival analysis, and univariate and multivariate analysis data. Additionally, for IHC, we attempted to retrieve information regarding phenotyping markers, antibodies, tissue microarray (TMA) versus whole sections, region of tumor analyzed, scoring method, cutoff values, and prognostic data for T cells. For bioinformatic studies, we attempted to retrieve the components of gene-expression signatures. Some publications presented data for multiple patient cohorts (e.g., different cancer types or histologic subtypes); in such cases, we assessed each cohort individually.

For the creation of Tables 1 and 2 and Fig. 1, studies that reported outcome based on multiple parameters were collapsed to one parameter based on the following rules. With regard to epithelial versus stromal location of TIL, priority was given (in order) to (i) epithelial plus stromal counts, (ii) epithelial counts, and (iii) stromal counts (giving priority to margin over peritumoral counts). For survival, most studies reported OS; therefore, this parameter was given priority over DSS and PFS. Supplementary Table S1 details which parameters were used for each study.

Findings

A total of 69 publications representing 19 cancer types met our search criteria (Supplementary Fig. S1). The majority of studies ($N = 53$) used IHC to detect TIL-B and/or PC, whereas 21 studies used bioinformatic approaches. We first review the IHC studies.

$CD20^+$ TIL

We first focused on the prognostic significance of $CD20^+$ TIL as determined by IHC, as this was the most commonly reported parameter (45 publications containing data on 54 cohorts representing 15 types of cancer). CD20 is expressed by B cells from early to late stages of differentiation but is downregulated upon differentiation into PC; therefore, CD20 is considered a marker of naïve and memory B cells. Of the 54 cohorts, the prognostic effect of $CD20^+$ TIL was positive in 27 (50.0%), neutral in 22 (40.7%),

Table 1. Summary of IHC-based $CD20^+$ TIL studies

		Prognostic effect (*N*)			
	Studies (*N*)	Positive	Negative	Neutral	References
Non–small cell lung cancer	8	4	1	3	11–17
Adenocarcinoma	2	1	1		16, 17
Breast cancer	7	5		2	18–21
Mixed subtypes	2	2			18, 19
ER negative	1	1			19
TNBC	1			1	20
Basal	1	1			19
HER2 positive	1	1			19
Invasive ductal	1			1	21
Colorectal cancer	5	3	1	1	22–26
Metastases	1	1			26
Hepatocellular carcinoma	5	2		3	27–31
Gastric cancer	5	2		3	32–36
Gastric cancer of the cardia	1			1	36
Ovarian cancer	5	2		3	37–39
Mixed subtypes	2	1		1	38, 39
HGSC	1	1			37
Endometrioid	1			1	37
Clear cell	1			1	37
Melanoma	4	2	1	1	40–43
Primary cutaneous	3	1	1	1	40–42
Metastases	1	1			43
Esophageal cancer	3	1		2	35, 44, 45
Mesothelioma	3	2		1	46, 47
Epithelioid	1	2			46, 47
Nonepithelioid	1			1	46
Pancreatic ductal adenocarcinoma	3	1	1	1	48–50
Oro- and hypopharynx	2	1	1		51
Low risk	1	1			51
High risk	1		1		51
Biliary tract cancer	1	1			52
Penile carcinoma	1			1	53
Prostate carcinoma	1			1	54
Soft tissue sarcoma	1	1			55
Total	54	27 (50.0%)	5 (9.3%)	22 (40.7%)	

Abbreviations: HGSC, high-grade serous ovarian cancer; TNBC, triple-negative breast cancer.

Table 2. Summary of IHC-based CD20$^+$ TIL studies by the methodologic approach

	Cohorts (*N*)	Prognostic effect (*N*)			*P*[a]	References
		Positive	Negative	No association		
Threshold for positivity					1.000	
Median	11	5	1	5		22, 27, 29, 30, 35, 36, 41, 43, 49
Positive vs. negative	5	3		2		37, 47, 52
Other	38	19	4	15		11–21, 23–26, 28, 31, 32, 34, 38–40, 42, 44–46, 48, 50, 51, 53–55
CD20$^+$ TIL location					0.365	
Intraepithelial	17	7		10		11, 14, 19, 23, 26, 27, 30, 31, 36, 37, 39, 41, 42, 47, 54
Stromal	18	8	2	9		14, 16, 19, 23, 26, 29–31, 33, 36, 41, 42, 47, 48, 50, 54
No region selection/full slide	33	18	4	11		13, 15, 17–22, 24–26, 32, 34, 35, 38, 40, 43–46, 49, 51–55
Not defined	2			2		12, 28
Tissue sample					0.719	
Full slide	21	12	2	7		11, 13, 15–18, 20, 22, 23, 26, 27, 29, 31–33, 40–42, 44, 48
TMA	33	15	3	15		12, 14, 19, 21, 24, 25, 28, 30, 34–39, 43, 45–47, 49–55
Cell-counting strategy					0.610	
Manual	38	18	3	17		11, 12, 14–16, 19, 21, 23–25, 29–31, 33, 35, 37–47, 50, 52–55
Digital	16	9	2	5		13, 17, 18, 20, 22, 26–28, 32, 34, 36, 48, 49, 51
Type of survival analysis					0.443	
OS	31	15	3	13		11, 12, 17, 18, 23–29, 31, 32, 34, 35, 38–47, 49, 50, 52, 53
DSS	19	9		10		11, 13, 14, 19–21, 30, 37, 38, 48, 53–55
PFS	16	6	3	8		11, 15–18, 22, 26, 29, 30, 33, 35, 36, 49, 51, 53
Multivariate analysis	17	10	2	5		14, 16, 17, 19, 24, 27, 29, 32, 33, 40, 43, 46–49, 52, 55

[a]Fisher exact test.

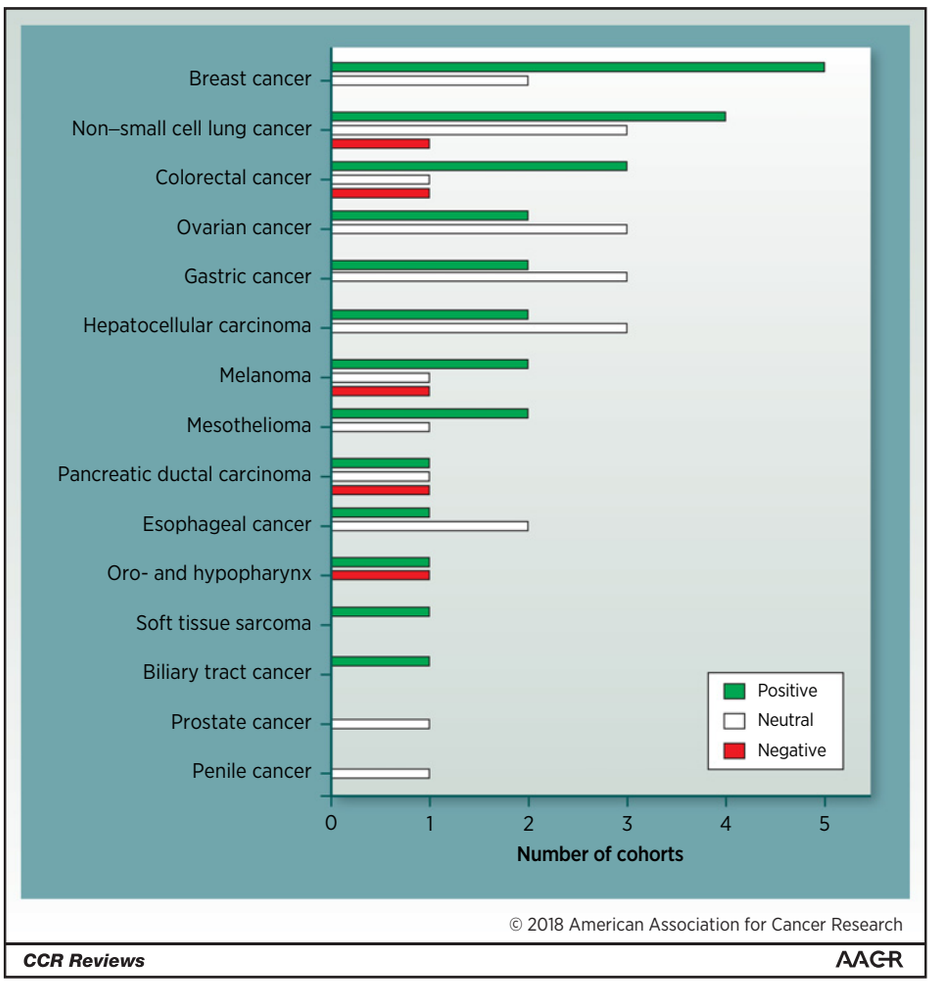


Figure 1.
Prognostic value of CD20$^+$ TIL according to cancer type. Bars represent the number of cohorts with positive (green), neutral (white), or negative (red) prognostic value for the indicated cancer types.

and negative in 5 (9.3%). We explored several possible explanations for these different prognostic effects, including both clinicopathologic and technical factors.

Clinicopathologic factors. *Cancer type.* It is now recognized that the prognostic effect of tumor-infiltrating T cells depends in part on cancer type (1); therefore, we assessed whether this factor was also relevant to $CD20^+$ TIL. The 54 cohorts we reviewed spanned a total of 15 tumor types (Table 1; Fig. 1). Within a given tumor type, discrepancies were commonly seen. For example, of the 7 breast cancer studies, 5 found a positive prognostic effect for $CD20^+$ TIL, whereas 2 found no significant effect (18–20). Another example is non–small cell lung cancer (NSCLC), where the prognostic effect ranged from positive (4/8 studies) to neutral (3/8) to negative (1/8; refs. 11–17).

We also considered whether tumor type might explain the 5 of 54 studies in which $CD20^+$ TIL showed a negative prognostic association. These studies spanned 5 tumor types: oro- and hypopharynx, NSCLC, colorectal cancer, pancreatic ductal adenocarcinoma (PDAC), and melanoma (16, 25, 40, 49, 51). For each of these tumor types, at least one other study found a positive or neutral prognostic association for $CD20^+$ TIL.

Overall, there was no example of a tumor type in which $CD20^+$ TIL were consistently associated with a positive, neutral, or negative prognostic effect across multiple studies (Fig. 1). Thus, the prognostic effect of $CD20^+$ TIL was not readily attributable to tumor type.

Histologic or molecular subtype. We also evaluated whether the prognostic effect of $CD20^+$ TIL was linked to the histologic or molecular subtype of a given cancer (Table 1). Milne and colleagues found that $CD20^+$ TIL had prognostic significance in the high-grade serous subtype of ovarian cancer (HGSC) but not in other histologic subtypes of ovarian cancer (37). Furthermore, $CD20^+$ TIL had prognostic significance in epithelioid mesothelioma, although no effect was found in the nonepithelioid type (46). On the other hand, Mahmoud and colleagues found prognostic benefit for $CD20^+$ TIL across three subtypes of breast cancer (ER^-, basal, and $HER2^+$; ref. 19). Most other studies pooled cancer subtypes, making it difficult to gain further insight into this potentially important parameter.

Grade and stage of tumors. Although most studies did not report subanalyses based on grade and stage, a study of oro- and hypopharynx cancer found that $CD20^+$ TIL had a positive prognostic effect in early disease but a negative effect in advanced disease (51).

Primary, previously treated, and metastatic tumors. The majority of studies (35/45) focused on samples obtained during primary surgery, before other treatments. Within this group, there were examples of positive, neutral, and negative prognostic effects. Of those studies that included samples from previously treated and/or metastatic tumors, most studies pooled these samples with those from primary disease, making it difficult to address the influence of this factor. One exception was a study of NSCLC, where $CD20^+$ TIL showed a positive association with survival irrespective of whether samples were obtained at primary surgery (early-stage disease) or after standard treatments (advanced-stage disease; ref. 13).

Technical factors. *Antibody.* The majority of $CD20^+$ TIL studies used the anti-CD20 antibody clone L26 ($N = 32/45$, 71.1%), whereas the remaining studies used clone BV11 ($N = 1$), or an unspecified antibody ($N = 12$). Given that the spread of prognostic effects within the L26 antibody group was similar to that of the full cohort, the antibody used does not seem to affect the direction of the prognostic outcome.

TMA or whole sections. The majority of cohorts (33/54, 61.1%) were analyzed by TMA, and the remainder used whole tissue sections. We found no significant difference in the sign of the prognostic effect between studies that used TMA and whole tissue sections ($P = 0.719$, Fisher exact test).

Region analyzed. The prognostic effect of tumor-infiltrating T cells and B cells frequently depends on their epithelial or stromal location; therefore, we considered this factor to the extent possible. We will use the term "intraepithelial" to refer to TIL described as having an epithelial location, and "stromal" to refer to TIL that were described with the terms stromal, peritumoral, or infiltrative margin. Seventeen studies reported results for intraepithelial $CD20^+$ TIL; of these, 7 reported a positive prognostic effect, and the remaining 10 found no prognostic association (Table 2). Eighteen studies reported results for stromal $CD20^+$ TIL; of these, 8 showed a positive prognostic effect, 9 showed no association, and 2 found a negative association. Thirty-three out of 54 cohorts made no distinction between intraepithelial and stromal $CD20^+$ TIL or reported a combined score for these two compartments. Of these, 18 reported a positive prognostic effect, 11 found no association, and 4 found a negative association. Finally, 2 studies did not state whether epithelial or stromal regions were evaluated; neither of these studies found a prognostic association for $CD20^+$ TIL. Overall, no clear differences were found in the direction of the prognostic effect based on whether the epithelial versus stromal location of $CD20^+$ TIL was considered ($P = 0.365$, Fisher exact test).

Counting strategy. Scoring of $CD20^+$ TIL was performed either manually (38/54) or digitally (16/54) using various software packages. No differences were found in the direction of the outcome data for either of these methods ($P = 0.610$, Fisher exact test).

Threshold for positivity. Various methods can be used to determine a cutoff value to stratify tumors as high versus low for $CD20^+$ TIL. The evaluated studies either calculated a cutoff value with a computer model or chose a threshold based on other reasons, which were often not reported (Table 2). Three studies used a threshold of 1 or more $CD20^+$ TIL, and 11 studies based their threshold on the median number of $CD20^+$ TIL. No significant differences in the direction of the prognostic effect were found based on the chosen cutoff method ($P = 1.000$ Fisher exact test).

Statistical methods of analysis. All studies used Kaplan–Meier survival analysis based on OS, DSS, and/or PFS. Thirty-one cohorts reported OS, 19 reported DSS, and 16 reported PFS. We found no differences in the direction of the prognostic effect based on the chosen outcome measures ($P = 0.443$ Fisher exact test).

Of the 32 cohorts that found a significant effect (positive or negative) of $CD20^+$ TIL in univariate analysis, 17 also performed multivariate analysis with standard clinicopathologic

parameters. The majority of these studies (12/17) found $CD20^+$ TIL to be an independent prognostic indicator (Table 2).

Other B-cell markers

CD19 is expressed at all stages of B-cell differentiation but lost upon final differentiation to PC. $CD19^+$ TIL were assessed in only one study, which found a positive association with OS in tongue squamous cell carcinoma (56).

All B-lineage cells, including PC, express CD79a. Three studies evaluated $CD79a^+$ TIL in addition to $CD20^+$ TIL, and all 3 studies found the two markers gave similar prognostic results (15, 31, 51).

Plasma cells

PC were assessed using a variety of markers, which we consider separately below.

CD138. CD138 (syndecan-1) was the most commonly used marker for assessing PC infiltrates by IHC. Within the hematopoietic compartment, CD138 is highly specific for PC; however, it can also be expressed by nonhematopoietic epithelial and stromal cells in the tumor microenvironment. Therefore, for the accurate definition of PC, it is advisable to have at least one other marker that confirms the hematopoietic origin of cells (57). This caveat notwithstanding, we reviewed 8 articles, reporting on 9 patient cohorts, which evaluated the prognostic effect of $CD138^+$ TIL (Fig. 2). One of these studies further defined PC as IgA^+CD138^+ cells, whereas the other studies scored immune-specific expression based on cell morphology, but did not describe how a correction was made for nonimmune CD138 expression. Four studies showed a positive prognostic effect of $CD138^+$ cells (colorectal cancer, esophageal and gastric cancer, and melanoma; refs. 24, 35, 43, 45), 2 studies found a neutral effect (esophageal cancer and NSCLC; refs. 12, 35), and 3 studies showed a negative effect (breast and ovarian cancers, and melanoma; refs. 21, 38, 58). Five of the studies that showed a significant prognostic effect on univariate analysis (3 positive studies and 2 negative studies) also performed multivariate analysis with clinicopathologic factors (21, 24, 38, 43, 45). $CD138^+$ TIL were an independent predictor of survival in 2 of 5 of these studies, predicting better outcome in melanoma (43) and worse outcome in ovarian cancer (38).

IGKC. The *IGKC* gene encodes the constant domain of immunoglobulin kappa-light chains and is highly expressed by PC. Therefore, for detection of PC by a single marker, IGKC might be preferable over CD138. We reviewed 6 studies (presenting data on 7 cohorts) in which $IGKC^+$ cells were detected by IHC (Fig. 2). In 5 of 7 cohorts, a positive prognostic effect was found (NSCLC, colorectal cancer, esophageal and two studies in breast cancer; refs. 12, 24, 35, 59, 60), although two studies found no association with survival (gastric and ovarian cancer) (35, 38). Four of the positive studies performed a multivariate survival analysis with clinicopathologic characteristics, and 3 of 4 found $IGKC^+$ cells to be an independent prognostic factor (NSCLC, esophageal, and breast cancer; refs. 12, 24, 35, 59).

Other Ig markers. A small number of studies have evaluated the prognostic significance of specific antibody isotypes (Fig. 2). $IgG4^+$ PC are associated with fibroinflammatory disease and may play an immunosuppressive role in cancer (61). Accordingly, $IgG4^+$ cells were found to have a negative prognostic effect in gastric cancer (62) and PDAC (63), but were not prognostic in NSCLC (16). Bosisio and colleagues found that IgA^+CD138^+ TIL were associated with poor prognosis in melanoma (58), which was opposite to the results reported when CD138 was used as a single marker in this setting (43). Finally, in NSCLC, both IgA^+ and IgM^+ cells lacked prognostic significance (16).

Tumor type	*N*	CD138	IGKC	IgG4	IgM	IgA	P63	CD20*	Ref. #
Breast cancer	338	■						□	21
Breast cancer	335		■						59
Breast cancer	330		■						60
Colorectal cancer	557	■	■					■	24
Esophageal cancer	210	■						□	45
Esophageal cancer	70	□	■					□	35
Gastric cancer	100	■	□					□	35
Gastric cancer	131			■					62
Melanoma	710	■†							58
Melanoma	147	■							43
Non–small cell lung cancer	350	□	■					□	12
Non–small cell lung cancer	114			□	□	□	■‡	■	16
Ovarian cancer	209	■	□					□	38
Pancreatic ductal adenocarcinoma	95			■					63

Figure 2.
Summary of IHC-based studies of PC. Boxes represent prognostic effect of indicated cell subset: positive (green), negative (red), no association (white). *N*, number of patients. *, For comparison, where available, CD20. TIL-B data are shown. †, $CD138^+IgA^+$ cells; ‡, $CD138^+P63^+$ cells.

p63. p63 is a rough endoplasmic reticulum–associated protein expressed highly on PC owing to their high secretory activity. Despite not finding a prognostic effect for IgA^+, $IgG4^+$, or IgM^+ cells (Fig. 2), Kurebayashi and colleagues found that $CD79a^+p63^+$ TIL were associated with poor prognosis in NSCLC (16).

Comparison of PC markers. In 5 studies, both $CD138^+$ and $IGKC^+$ cells were assessed, providing an opportunity to compare their prognostic effects (Fig. 2; refs. 12, 24, 35, 38). In 2 of 5 studies, $IGKC^+$ cells were associated with a positive prognostic effect, whereas $CD138^+$ cells showed no significant association with outcome (12, 35). In two other studies, $CD138^+$ cells showed a positive (35) or negative (38) prognostic effect, whereas $IGKC^+$ cells were neutral. Only 1 of 5 studies found a concordant prognostic effect (positive) for $CD138^+$ and $IGKC^+$ cells (colorectal cancer; ref. 24).

Prognostic significance of CD138 and IGKC compared with CD20

Only 7 studies evaluated both $CD20^+$ TIL and PC (using CD138 in 7/7 studies and IGKC in 5/7 studies, Fig. 2; refs. 12, 21, 24, 35, 38, 45). The prognostic effect of $CD20^+$ TIL was positive in 1 and neutral in 6 of these studies. By comparison, $CD138^+$ cells were positive in 3, neutral in 2, and negative in 2 of the 7 studies, and $IGKC^+$ cells were positive in 3 and neutral in 2 of 5 studies. These very limited data suggest that PC might have a more favorable prognostic effect than $CD20^+$ TIL; however, further assessment of this issue is clearly warranted.

Prognostic significance of TIL-B relative to T cells

Although tumor-infiltrating T cells are considered a positive prognostic factor for most cancers, there are some exceptions (1). Therefore, for studies that evaluated both T cells and $CD20^+$ TIL, we assessed whether there was concordance regarding their respective prognostic effects. For 31 cohorts, there were matched data provided for $CD20^+$ and $CD8^+$ TIL (Fig. 3). The prognostic effect of $CD20^+$ TIL was positive in 48.4% (15/31) of these cohorts, neutral in 41.9% (13/31), and negative in 9.7% (3/31). Similarly, the prognostic effect of $CD8^+$ TIL was positive in 41.9% (13/31), neutral in 51.6% (16/31), and negative in 6.5% (2/31) of these cohorts. The prognostic effects of CD20 and CD8 were concordant in 54.8% (17/31) of cohorts, and these concordant results were roughly equally divided between positive (9/17 cohorts) and neutral (8/17 cohorts) prognostic effects. The discordant results were roughly equally divided between $CD20^+$ TIL being more favorable than $CD8^+$ TIL (8/14 of cohorts) and $CD8^+$ TIL being more favorable than $CD20^+$ TIL (6/14 of cohorts).

A similar pattern was seen in the 24 cohorts that evaluated both $CD3^+$ and $CD20^+$ TIL (Fig. 3). The prognostic effect of $CD20^+$ TIL was positive in 41.7% (10/24), neutral in 50.0% (12/24), and negative in 8.3% (2/24) of these cohorts. Similarly, the prognostic effect of $CD3^+$ TIL was positive in 33.3% (8/24), neutral in 54.2% (13/24), and negative in 12.5% (3/24) of these cohorts. The prognostic effects of CD20 and CD3 were concordant in 62.5% (15/24) of cohorts, and these concordant results were roughly equally divided between positive (6/15 cohorts) and neutral (8/15 cohorts) prognostic effects, with one cohort showing a concordant negative effect. The discordant results were divided between $CD20^+$ TIL being more favorable than $CD3^+$ TIL (6/9 of cohorts) and $CD3^+$ TIL being more favorable than $CD20^+$ TIL (3/9 of cohorts).

Thus, the prognostic effects of tumor-infiltrating B cells and T cells were concordant in at least half the cohorts and, when discordant, showed no clear bias toward T cells or B cells being more favorable.

Combined analysis of T-cell and B-cell infiltrates

A small number of studies evaluated the combined prognostic effect of T-cell and B-cell infiltrates. In HGSC, the presence of both $CD20^+$ and $CD8^+$ TIL was associated with longer DSS compared with CD8 TIL alone (64). The prognostic effect was further strengthened when PC infiltrates were also taken into account (65). In hepatocellular carcinoma (HCC), patients with both $CD3^+$ and $CD20^+$ TIL had a more favorable prognosis than those with only one of these TIL subsets (27). Accordingly, in a second HCC cohort, $CD8^+$ TIL were only prognostic if $CD20^+$ TIL were also present (29). Likewise, in PDAC, aggregates of $CD20^+$ TIL increased the prognostic effect of $CD8^+$ TIL (48).

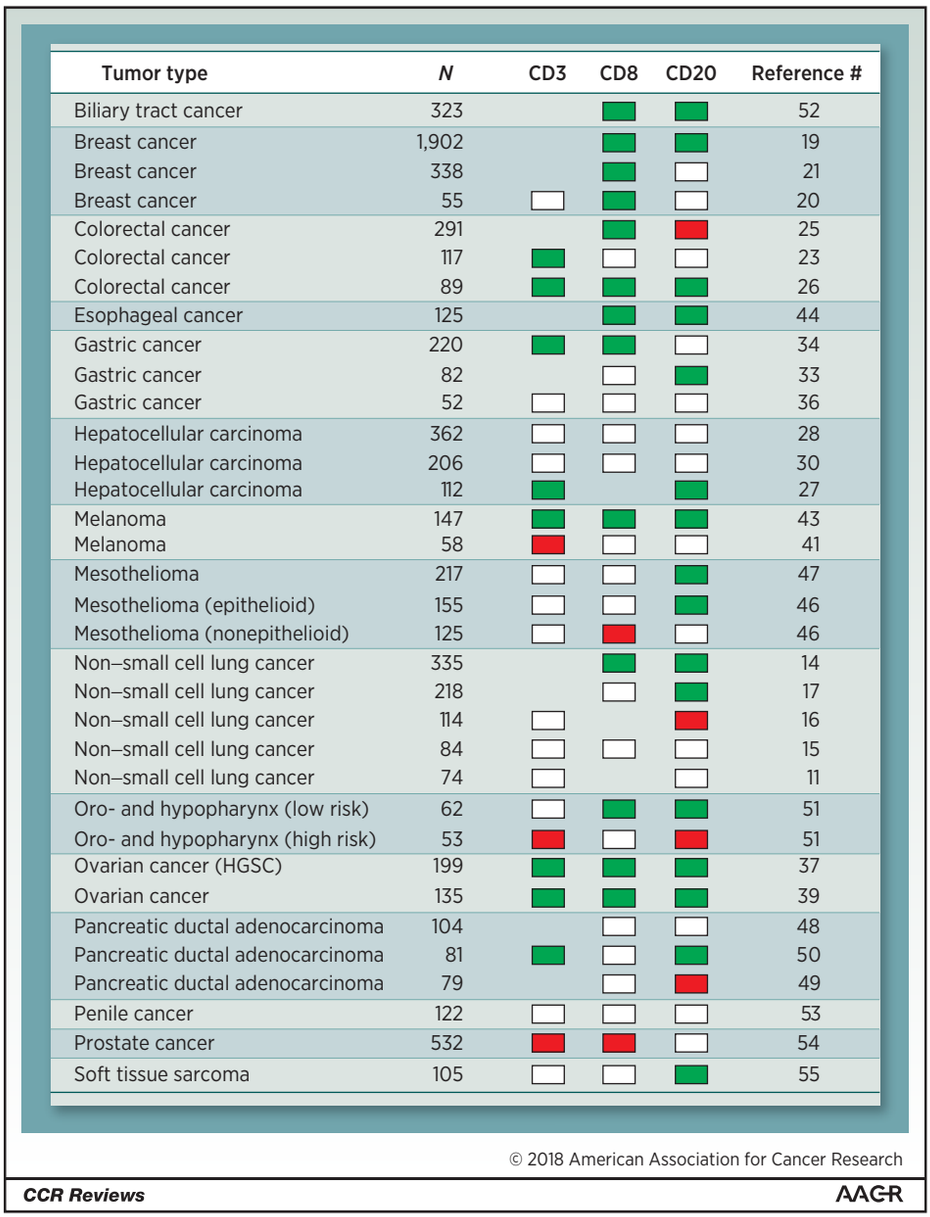
Bioinformatic studies assessing TIL-B and PC

We also reviewed 21 studies that used bioinformatic approaches to infer the presence of TIL-B and PC (Supplementary Table S2). We restricted our analysis to studies that reported the use of B-cell–specific gene-expression signatures, although in the majority of cases these overlapped with signatures from T cells or other immune cells, making it difficult to infer the independent contribution of TIL-B. The most commonly used signature genes for B cells and PC were immunoglobulin genes, especially *IGKC*. Other common signature genes included *CD19*, *MS4A1*, *CD79A*, and *CXCL13*. Three studies used CIBERSORT gene signatures (66) to infer the presence of various TIL-B subsets ranging from naïve B cells to fully differentiated PC (67–70).

The majority of bioinformatic studies focused on breast cancer ($n = 14$). An early report by Schmidt and colleagues demonstrated an association between a B-cell metagene signature and increased metastasis-free survival (MFS) in node-negative, proliferation-high breast cancers (71). Similarly, Bianchini and colleagues found a positive association between a B-cell/PC metagene and MFS in highly proliferative ER^+ breast cancers, as well as ER^- breast cancers (72). Other studies have also reported positive prognostic associations for a variety of B-cell/PC gene signatures applied to the different subtypes of breast cancer (60, 67–69, 73–80).

In addition to breast cancer, B-cell and/or PC signatures have been associated with favorable outcomes in lung (15, 67, 70), colorectal (81), gastric (33), ovarian (65, 78), and hepatocellular (31) cancers, and cutaneous melanoma (82).

Several groups have used B-cell and/or PC gene signatures in pan-cancer analyses. Schmidt and colleagues found that a single immunoglobulin gene, *IGKC*, was associated with positive prognosis in breast, lung, and colorectal cancers (60). Gentles and colleagues reported that a PC gene signature was a significant predictor of survival across diverse solid tumors, including breast and lung adenocarcinomas (67). Iglesia and colleagues evaluated several published B-cell/PC signatures across 11 cancer types (79). Consistent with other studies, they found that B-cell signatures were associated with increased OS across many tumor types, including melanoma and breast and lung cancer. Conversely,



Tumor type	*N*	CD3	CD8	CD20	Reference #
Biliary tract cancer	323		+	+	52
Breast cancer	1,902		+	+	19
Breast cancer	338		+		21
Breast cancer	55		+		20
Colorectal cancer	291		+	−	25
Colorectal cancer	117	+			23
Colorectal cancer	89	+	+	+	26
Esophageal cancer	125		+	+	44
Gastric cancer	220	+	+		34
Gastric cancer	82			+	33
Gastric cancer	52				36
Hepatocellular carcinoma	362				28
Hepatocellular carcinoma	206				30
Hepatocellular carcinoma	112	+		+	27
Melanoma	147	+	+	+	43
Melanoma	58	−			41
Mesothelioma	217			+	47
Mesothelioma (epithelioid)	155			+	46
Mesothelioma (nonepithelioid)	125		−		46
Non–small cell lung cancer	335		+	+	14
Non–small cell lung cancer	218			+	17
Non–small cell lung cancer	114			−	16
Non–small cell lung cancer	84				15
Non–small cell lung cancer	74				11
Oro- and hypopharynx (low risk)	62		+	+	51
Oro- and hypopharynx (high risk)	53	−		−	51
Ovarian cancer (HGSC)	199	+	+	+	37
Ovarian cancer	135	+	+	+	39
Pancreatic ductal adenocarcinoma	104				48
Pancreatic ductal adenocarcinoma	81	+		+	50
Pancreatic ductal adenocarcinoma	79			−	49
Penile cancer	122				53
Prostate cancer	532	−	−		54
Soft tissue sarcoma	105			+	55

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Figure 3.
Summary of studies with combined analysis of T-cell and B-cell infiltrates. Boxes represent prognostic effect of the indicated TIL subset: positive (green), negative (red), and no association (white). *N*, number of patients.

negative associations were seen for glioblastoma and renal cancer. Their work also revealed the limitations of bioinformatic approaches in that different B-cell signatures (and other immune cell signatures) often yielded different prognostic results within the same tumor type. For example, applying CIBERSORT to different subtypes of breast cancer, Ali and colleagues found that the prognostic effect of B-lineage cells varied from neutral to positive depending on tumor subtype and the specific B-cell signature used (68).

In summary, the majority of bioinformatic analyses demonstrated a positive or neutral prognostic effect for TIL-B and PC. However, by the nature of such analyses, overlapping signatures from T cells and other immune cells were a common confounding factor. Moreover, the results were often dependent on the specific B-cell signature used. Nonetheless, there were relatively few examples of negative prognostic effects of TIL-B and PC.

Discussion

To address current uncertainties regarding the contribution of B-lineage cells to antitumor immunity, we conducted a systematic review of 69 studies addressing the prognostic significance of TIL-B and PC across 19 human cancers. Most studies reported a positive or neutral prognostic effect for TIL-B and/or PC, with only a small minority reporting a negative effect. In studies that assessed both B cells and T cells, the prognostic effects of the two TIL subsets were largely concordant; where the effects were discordant, there was no clear bias toward B cells or T cells being more favorable.

Moreover, the prognostic effect of $CD3^+$ and/or $CD8^+$ TIL was generally higher when TIL-B and/or PC were present. These results are in accord with studies assessing the prognostic value of tertiary lymphoid structures (TLS), lymph node–like structures that contain T cells, B cells, and PC and are associated with strong TIL responses (83). Collectively, these studies suggest that B-lineage cells collaborate with T cells to promote antitumor immunity.

There are several theoretical ways in which T cells, B cells, and PC could functionally interact in the tumor microenvironment (Fig. 4; refs. 84, 85). TIL-B could stimulate tumor-specific T cells directly through the production of immunostimulatory cytokines (e.g., lL2, IL4, IFNγ, and TNFα; refs. 86, 87) and indirectly by serving as antigen-presenting cells to T cells (88). Additionally, PC could produce tumor-specific antibodies that, upon binding to tumor cells, inhibit their target proteins, activate complement, and/or promote antibody-dependent cellular cytotoxicity (ADCC). In cases where TIL-B are associated with poor prognosis, the B-cell response may be skewed toward a regulatory (Breg) phenotype. Indeed, Bregs are found in diverse physiologic contexts and can inhibit $CD8^+$ T-cell responses through the production of suppressive cytokines (e.g., IL10, IL35, and TGFβ) and the recruitment of regulatory T cells (Tregs) to the tumor microenvironment (89). Despite these theoretical possibilities, the precise functions of TIL-B and PC in the tumor microenvironment remain poorly understood.

Our analysis yielded several insights that may facilitate further progress on this subject:

1. There is a clear need for markers to distinguish effector from regulatory B-lineage cells by multiplex IHC or analogous methods. This may become possible through improved antibodies or methods to detect phenotype-defining transcription factors or cytokines (e.g., IFNγ versus IL10) in tissue sections.
2. Our analysis suggested PC carry greater prognostic significance than TIL-B, yet there are major gaps in our understanding of this subset. At a minimum, more data are needed regarding the prognostic significance of PC in various cancer types. For this, we recommend using a simple, robust dual stain for CD20 and CD79a, which allows simultaneous detection of PC ($CD20^-CD79a^+$) and B cells ($CD20^+CD79a^+$). We also need to define the antigens recognized by PC-derived antibodies; while initial progress has been made in lung cancer (13), our knowledge is far from complete.
3. Given the initial indications that IgG4 may be negatively associated with prognosis (62, 63), together with prior reports of an immunosuppressive role for this Ig isotype

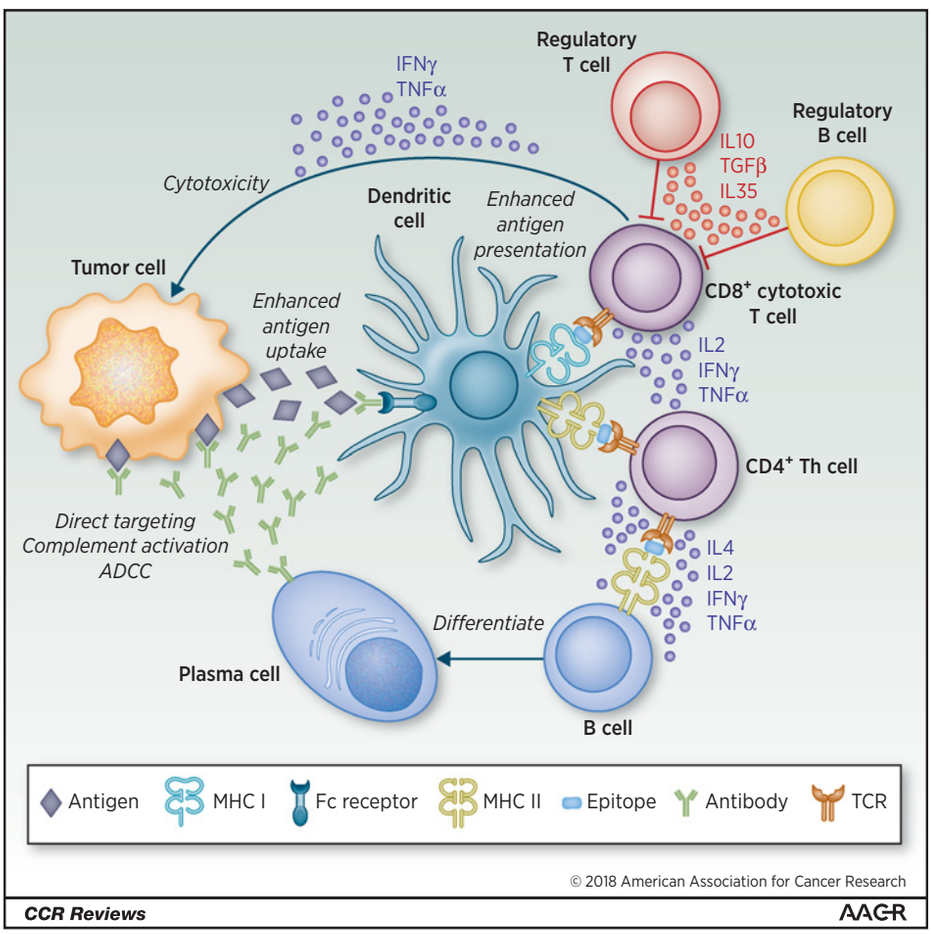

Figure 4.
Schematic overview of known and hypothesized functional interactions between B cells, PC, and T cells in the tumor microenvironment. B cells can enhance T-cell responses by producing stimulatory cytokines and chemokines. They can also differentiate into PC, which may produce antibodies against tumor-associated antigens. These in turn may have direct effects against their target proteins, trigger complement or antibody-dependent cellular cytotoxicity (ADCC) reactions, or enhance antigen presentation to T cells through Fc receptor–mediated mechanisms. Conversely, regulatory B cells can act in concert with regulatory T cells to suppress antitumor immune responses.

(61), additional prognostic studies with this marker are warranted.

4. It will be important to assess TIL-B and PC in the context of T cell subsets (including cytotoxic T cells, Tregs, Th1/Th2/Th17 subsets, and others) and other immune cells in the tumor microenvironment, as this undoubtedly influences their functional attributes.
5. Most studies to date have not addressed the influence of histologic and/or molecular subtype on the prevalence and prognostic effect of TIL-B or PCs. For example, in breast cancer, $CD20^+$ TIL were prognostically favorable in the ER^-, $HER2^+$, and basal-like subtypes, but not the triple-negative breast cancer (TNBC) subtype (19, 20), which may provide clues regarding the underlying immunologic processes. Future studies should consider the relevant histologic and molecular subtypes for a given cancer and use multivariate analyses to account for their potential influence.
6. Another understudied issue is the impact of standard treatment (e.g., surgery, chemotherapy, and radiation) on the functional properties and prognostic significance of TIL-B and PC. For example, increased $CD20^+$ TIL densities were observed after neoadjuvant chemotherapy in ovarian cancer (90), and chemoradiation-induced ulcers in esophageal cancer exhibited higher levels of $IgG4^+$ PC (91). Most studies to date have used primary, untreated tumor samples, so more research is needed involving posttreatment and relapsed samples.
7. Finally, to enable mechanistic studies, there is a clear need for animal models in which TIL-B, PC, and TLS arise spontaneously and can be experimentally manipulated.

On balance, our findings suggest that B-lineage cells play a beneficial role in the majority of cancer types, suggesting that a goal of immunotherapy should be to enhance rather than inhibit their activity. Potential immunotherapy strategies include the use of B-cell–stimulating cytokines (e.g., IL21; ref. 92) or agonists (e.g., CD40 ligand; ref. 93), or the blockade of inhibitory signals through pathways such as PD-1/PD-L1, which is highly relevant to interactions between PC and T follicular helper cells (94). Furthermore, there is some evidence to support the use of tumor-specific B cells for adoptive cell therapy (95, 96). Further research is clearly warranted to find the most effective ways to engage TIL-B and PC so that patients receive the benefits of coordinated, multifaceted antitumor immune responses.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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