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Review

Prognostic value of CD163^{+} macrophages in solid tumor malignancies: A scoping review

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ABSTRACT

Tumor-associated macrophages (TAMs) play crucial roles in development and progression of malignant diseases. Notably, CD163^{+} TAMs likely perform specific pro-tumorigenic functions, suggesting that this subset may serve as both prognostic biomarkers and targets for future anti-cancer therapy.

We conducted a scoping review to map the current knowledge on the prognostic role of CD163^{+} TAMs in the five most lethal cancers worldwide: Lung, colorectal, gastric, liver, and breast cancer. For all cancer types, most studies showed that high tumoral presence of CD163^{+} cells was associated with poor patient outcome, and this association was more frequently observed when CD163^{+} cells were measured at the tumor periphery compared to more central parts of the tumor.

These results support that CD163^{+} TAMs represent a biomarker of poor patient outcome across a variety of solid tumors, and highlight the relevance of further investigations of CD163^{+} TAMs as targets of future immunotherapies.

1. Introduction

Immune cells play critical roles in the development and progression of malignant diseases [1]. The cancer immunology field has evolved rapidly in the past decades, and "tumor-promoting inflammation" along with "tumor immune evasion" are now considered hallmarks of cancer [2,3].

Macrophages are vital in shaping immune responses in health and disease [4], and are among the most abundant non-cancerous cells in tumors, constituting up to 50% of the tumor mass in some cases [5,6]. Notably, a high infiltration of macrophages has been associated with poor patient outcomes in several human malignancies [7]. However, associations between high macrophage infiltration and favorable outcomes have also been reported, mainly in colorectal cancer [7–10]. As outlined below, there is an increasing focus on macrophage heterogeneity in tumors, with investigations of the prognostic impact and functions of specific macrophage subsets not limited to the traditional M1/M2 paradigm. This pronounced diversity of macrophages in the tumor microenvironment (TME) calls for therapeutic strategies targeting specific subsets of macrophages [11,12]. Importantly, recent studies have drawn attention to CD163^{+} macrophages as a potential target for future macrophage-directed anti-cancer therapy [12–18]. To our knowledge, this is the first review focused specifically on the prognostic role of CD163^{+} macrophages across multiple solid tumor malignancies in humans.

Macrophages contribute to multiple pro-tumor hallmark capabilities but can also antagonize tumor development and progression [2,12,19]. The tumor-promoting functions of tumor-associated macrophages (TAMs) have been widely described and include the support of cancer cell survival and proliferation, angiogenesis, immune suppression, resistance to anti-cancer therapy, and ultimately metastasis [19–22]. Due to these critical roles in tumor development and progression, TAMs

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are attractive targets for future immunomodulatory anti-cancer therapy [11,12,22,23]. Treatment strategies currently in clinical trials are mainly focused on pan-depletion of TAMs by inhibiting the CSF-1/CSF-1R axis or blocking CCR2/CCL2 signaling. However, these strategies have shown limited clinical benefit despite promising pre-clinical results [11,24]. Notably, recent single-cell analyses have revealed an unprecedented heterogeneity among macrophages in human tumors [25–27]. Further research is warranted to determine the functions of specific TAM subsets and the implications for treatment response and patient outcome, but it seems likely that different subsets of TAMs play distinct roles in the TME [11,24]. In combination with the limited clinical effects of pan-depleting strategies, this highlights the need for designing and exploring the impact of therapies targeting specific subsets of TAMs [11,12].

Recent studies have demonstrated that the hemoglobin-haptoglobin (Hb-Hp) scavenger receptor CD163 can serve as an effective gateway receptor for targeting drugs to TAMs [13,14,16,28]. The CD163 receptor is a specific marker of human monocytes and macrophages [29,30], and importantly, the expression of CD163 is increased on pro-tumoral TAMs [19,31]. In a recent study using a mouse model of melanoma, targeted depletion of $CD163^{+}$ TAMs resulted in infiltration of activated T cells and markedly reduced tumor growth, whereas pan-depletion of TAMs abrogated the therapeutic effects [13]. Another study using a mouse model of metastatic ovarian cancer showed that specific depletion of $CD163^{+}$ TAMs prevented tumor progression and metastatic spread [14]. In addition, a recent study identified a distinct population of TAMs with high expression of heme oxygenase-1 (HO-1) that plays critical roles in shaping a pro-metastatic TME by promoting immune suppression, angiogenesis, and epithelial-to-mesenchymal transition through heme catabolism and subsequent generation of carbon monoxide (Fig. 1). Importantly, this subset of $HO\text{-}1^{hi}$ TAMs showed increased expression of CD163, supporting that CD163-mediated Hb-Hp endocytosis functions as the primary route of heme feeding [32]. In line with this, a small subset of $CD163^{hi}$ macrophages has been shown to drive resistance against vaccine-induced tumor regression in preclinical models. This subset displayed a strong anti-inflammatory wound healing signature with high expression of HO-1. Notably, the study indicated that the $CD163^{hi}$ macrophages utilized downstream effects of HO-1 to suppress $CD8^{+}$ T cell activity as a mechanism of treatment resistance. Depletion of the $CD163^{hi}$ macrophage subset strongly improved vaccine-induced tumor control [15].

Overall, these studies emphasize the importance of considering TAM heterogeneity in developing targeted therapies and indicate that the $CD163^{+}$ TAM subset plays critical tumor-promoting roles in the TME. Accordingly, $CD163^{+}$ TAMs may be a favorable target for novel anti-cancer immunotherapy. Furthermore, owing to recent drug delivery advancements, specific targeting of $CD163^{+}$ TAMs in cancer patients may be within reach, e.g., by exploiting a lipid nanoparticle-based drug delivery platform as depicted in Fig. 1 [13,14,16,28,33]. Therefore, we decided to examine the prognostic role of $CD163^{+}$ TAMs in the most lethal solid tumor malignancies in humans.

We conducted a scoping review to identify and compile current knowledge on the prognostic role of $CD163^{+}$ TAMs in the five types of cancer with the highest number of deaths worldwide in 2022: Lung cancer, colorectal cancer, gastric cancer, liver cancer, and breast cancer [34]. We identified the scoping review as the most appropriate format for mapping all peer-reviewed reports on the prognostic role of $CD163^{+}$ TAMs [35,36]. The purpose was to reveal the extent of relevant literature, to provide an overview of results from the included reports, and to discuss the methodologies used in the published literature, especially focusing on $CD163^{+}$ cell counts in tumors, including different histopathological localizations, as this has been shown to affect the association between TAM presence and survival [10].

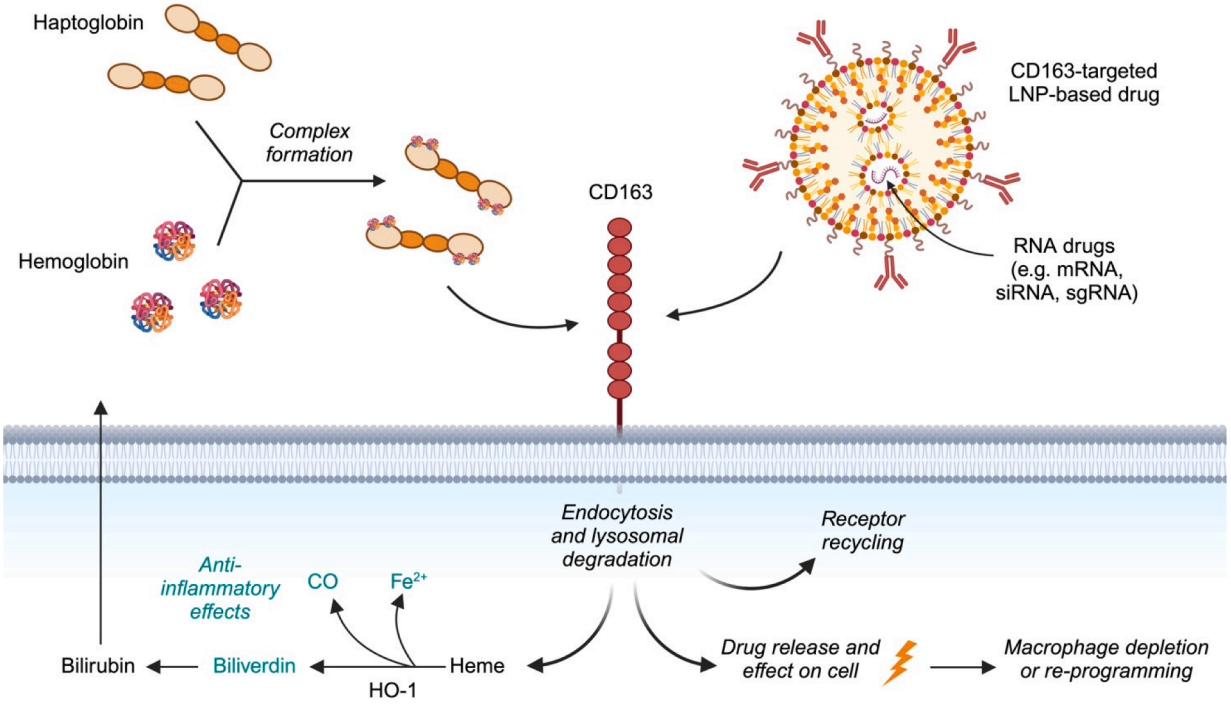

Fig. 1. Schematic drawing of the surface membrane of a macrophage with CD163 expression. The left side of the figure illustrates CD163-mediated scavenging of hemoglobin (Hb), which is a known biological function of the CD163 receptor. Hemoglobin is released to the circulation upon hemolysis, and is rapidly bound by haptoglobin (Hp) forming the Hb-Hp complex which binds to the CD163 receptor followed by endocytosis and lysosomal degradation. Heme is subsequently degraded by heme oxygenase-1 (HO-1), hereby producing the anti-inflammatory metabolites Fe^{2+}, carbon monoxide (CO), and biliverdin. Biliverdin is converted to bilirubin before being secreted from the cell [18]. The right side of figure illustrates how a lipid nanoparticle (LNP)-based drug delivery platform may be utilized to target the CD163 receptor with the aim of depleting or re-programming $CD163^{+}$ macrophages to induce anti-tumor immunity as a novel therapeutic anti-cancer strategy.

2. Methods

2.1. Search strategy and identification of eligible studies

The present review was conducted according to a predetermined protocol based on the PRISMA-ScR statement [37]. Eligible studies were identified by searching PubMed, Embase, Scopus, and Web of Science for reports published in English up to and including the 1st of July 2024. We conducted five separate searches, all consisting of four blocks. Blocks 1 to 3 were identical in all five searches, whereas Block 4 contained relevant terms for the specific type of cancer. Only carcinomas were included. Intrahepatic cholangiocarcinoma was also included in liver cancer. The search blocks and terms are shown in Table 1. The exact search strings in each database can be found in Sup. Table 1.

Two reviewers independently examined all search results (HM and KJM). After removing duplicates, all abstracts were screened, and some reports were excluded before the full texts of the remaining reports were assessed for eligibility (Fig. 2). This selection was done according to our predetermined inclusion and exclusion criteria (see below). In case of disagreement between the two reviewers, a third reviewer (MNA) settled the question.

2.2. Inclusion criteria

The predetermined criteria for inclusion of a study were as follows:

1) The study included $\geq$ 20 patients with proven diagnoses of either lung cancer, colorectal cancer, gastric cancer, liver cancer, or breast cancer.
2) The study had available information on the degree of $CD163^+$ (protein or mRNA expression) cell presence at the primary tumor site (tumoral or peritumoral tissue) in relation to patient survival time and/or time to disease relapse or progression.

2.3. Exclusion criteria

The predetermined exclusion criteria were as follows:

1) Other language than English.
2) Non-peer-reviewed reports.
3) Reviews and meta-analyses.
4) Non-primary data (e.g., data from publicly available databases).
5) Duplicate patient data. When the same patient cohort was used in more than one study, the study placing the highest emphasis on CD163 as a predictive marker of survival was included.
6) Cell subsets defined by the expression of more than one marker in addition to CD163; e.g., a comparison of high vs. low tumoral presence of $CD68^+CD163^+$ cells was included in the study, whereas studies using more than two markers (CD163 included) to define the cell subset were excluded.

2.4. Data extraction and definitions

We extracted relevant information on the patient cohorts from each study. This extraction included the country in which patient inclusion was conducted, the number of patients included in the appropriate analyses, and the investigated patient outcomes (overall survival (OS), disease-free survival (DFS), disease-specific survival (DSS), and progression-free survival (PFS)). We included recurrence-free/relapse-free survival (RFS) and distant relapse-free survival (DRFS) in the DFS group. In addition, we collected relevant information on the assessment of CD163 expression in the individual studies. This information included the method used to evaluate the expression of CD163 (immunohistochemistry (IHC), immunofluorescence (IF), or reverse transcription polymerase chain reaction (RT-PCR)), including the clone of anti-CD163 antibody used for IHC or IF, and the cut-off that was used to distinguish between a high and low CD163 expression. Furthermore, we noted the histopathological components and/or spatial localizations within the primary tumor and/or peritumoral tissue in which CD163 was measured. Histopathological components refer to tumor epithelium and tumor-related stroma, while spatial localizations refer to e.g., intratumoral area, invasive front, and peritumoral tissue. In the remaining review, these components/localizations will be referred to as "histopathological localization".

We assigned an "overall result" to each report (for univariate and multivariate analyses, respectively, when available) based on predetermined definitions of three different categories:

1) "Poor outcome" was assigned when a high tumoral/peritumoral presence (referred to as high tumoral presence in the remaining review) of $CD163^+$ cells showed a statistically significant association with shorter survival.
2) "Favorable outcome" was assigned when a high tumoral presence of $CD163^+$ cells showed a statistically significant association with longer survival.
3) "Non-significant outcome" was assigned when no statistically significant association between tumoral presence of $CD163^+$ cells and survival was observed.

A p-value $\leq$ 0.05 was considered statistically significant. Some of the included reports investigated the presence of $CD163^+$ cells in various histopathological localizations of the tumor. In some cases, these reports showed a statistically significant association between high CD163 and survival in one location but no significant association in another location. In this case, the significant result determined which "overall result" that was assigned to the report. Two reports showed an association with poor outcome in one location and favorable outcome in another location [38,39]. These two articles have been counted twice when calculating the distribution of reported patient outcomes. Other sub-analyses (e.g., lymph node status, hormone receptor status, etc.) were not considered when assigning "overall results" to the reports. Lastly, we aimed to provide an overview of reported patient outcomes in different histopathological localizations of the tumors to assess the impact of spatial

Table 1
Search strings for each of the five types of cancer: Lung cancer, colorectal cancer, gastric cancer, liver cancer, and breast cancer. Block 1 to 3 were identical for all types of cancer. Only Block 4 differed in the search strings. The search blocks were separated with AND in the search strings.

Block 1		Block 2		Block 3		Block 4
Macrophag*	**AND**	CD163	**AND**	Survival OR prognostic OR prognosis OR outcome	**AND**	"Lung cancer" OR "lung carcinoma"
						"Colorectal cancer" OR "colorectal carcinoma" OR "colon cancer" OR "rectal cancer" OR "colon carcinoma" OR "rectal carcinoma"
						"Gastric cancer" or "gastric carcinoma"
						"Liver cancer" OR "hepatocellular carcinoma" OR "intrahepatic cholangiocarcinoma"
						"Breast cancer" OR "breast carcinoma"

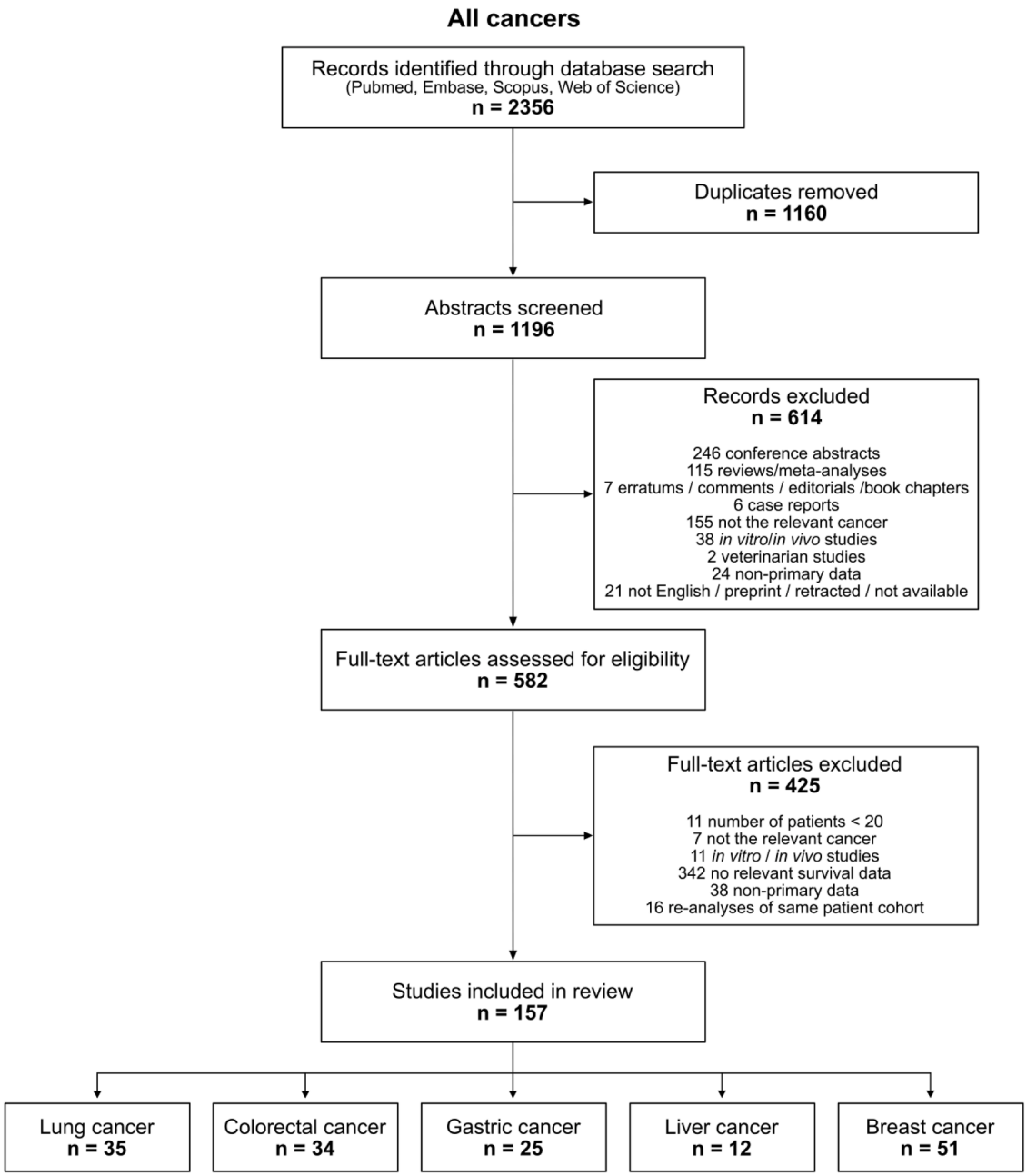

Fig. 2. PRISMA flowchart. Flowchart showing the summarized article selection process for all five types of cancer. Separate flowcharts for lung cancer, colorectal cancer, gastric cancer, liver cancer, and breast cancer can be seen in Sup. Fig 1.

heterogeneity on reported patient outcome. These findings are described in further detail in Section 3.4.

3. Results

3.1. Search results

The article selection was performed separately for each of the five types of cancer (lung, colorectal, gastric, liver, and breast cancer) based on the corresponding search string. These five search strings were used to search in Pubmed, Scopus, Embase, and Web of Science, which resulted in identifying 2356 articles across all cancer types. The PRISMA flowchart (Fig. 2) summarizes the article selection process for all five types of cancer. The flowchart shows the number of articles excluded at each step (duplicate removal, abstract screening, full-text assessment), including the reason for excluding the articles. A total of 157 articles were finally included in the present scoping review (35 lung cancer [39–73], 34 colorectal cancer [74–107], 25 gastric cancer [38, 108–131], 12 liver cancer [132–143], and 51 breast cancer articles [144–194]). Flowcharts for each type of cancer separately can be seen in Sup. Fig. 1.

3.2. Study characteristics

A total of 157 studies reporting data on 38,514 patients (7127 lung cancer, 12,240 colorectal cancer, 5139 gastric cancer, 1388 liver cancer, and 12,620 breast cancer) were included in our scoping review. All manuscripts were published in the years 2007 to 2024. Characteristics of the included studies are shown in Table 2. Extracted data from each study can be seen in Sup. Table 2.

Table 2
Characteristics of included studies. IHC: Immunohistochemistry. IF: Immunofluorescence. RT-PCR: Reverse transcription polymerase chain reaction. OS: Overall survival. DFS: Disease-free survival. DSS: Disease-specific survival. PFS: Progression-free survival. *One study included patient cohorts from two different continents, and the sum of percentages is therefore > 100%. **Most studies evaluated more than one survival time parameter, and the sum of percentages is therefore > 100%.

Characteristics	Number of studies (% of total number of studies)
Type of cancer	
Lung cancer	35 (22%)
Colorectal cancer	34 (22%)
Gastric cancer	25 (16%)
Liver cancer	12 (8%)
Breast cancer	51 (32%)
Continent*	
Asia	94 (60%)
Europe	49 (31%)
North America	9 (6%)
Other	6 (4%)
Method used to detect CD163$^+$ cells	
IHC/IF	153 (97%)
RT-qPCR	3 (2%)
Not available	1 (<1%)
Clone of anti-CD163 antibody	
10D6	73 (48%)
MRQ-26	13 (8%)
EPR19518	11 (7%)
D6U1J	3 (2%)
EDHu-1	2 (1%)
OTI1B4	2 (1%)
EPR14643	2 (1%)
EP324	2 (1%)
OTI2G12	1 (<1%)
RM3/1	1 (<1%)
GHI/61	1 (<1%)
Polyclonal	7 (5%)
Clone not reported	35 (23%)
Cut-off between high and low tumoral presence of CD163$^+$ cells	
Median or mean	68 (43%)
Other cut-offs, including various scoring systems and percentiles (see Sup. Table 2)	75 (48%)
Evaluation of CD163 as a continuous variable	2 (1%)
Not available	12 (8%)
Survival parameter(s)**	
OS	116 (74%)
DFS	78 (50%)
DSS	21 (13%)
PFS	12 (8%)
Not available	4 (3%)

The studies were conducted in 27 countries, with most patient cohorts representing Asia (60%, $n = 94$). Almost all studies (97%, $n = 153$) used IHC or IF to characterize the tumoral presence of CD163$^+$ cells. Clone 10D6 was the most common (48%, $n = 73$) clone of anti-CD163 antibody used in the included studies. Notably, 23% ($n = 35$) of the studies did not specify the used clone of antibody. The remaining clones are summarized in Table 2. Almost half of the studies (43%, $n = 68$) used the median or mean of their respective quantifications of CD163$^+$ cells (e.g., absolute count, density, etc.) as the cut-off to distinguish between high and low presence of CD163$^+$ cells in tumors. Accordingly, approximately half of the studies used other cut-off parameters, including various scoring systems and percentiles (see Sup. Table 2).

3.3. Patient outcome

To evaluate the distribution of reported associations between a high tumoral presence of CD163$^+$ cells and patient outcome, we assigned an overall result (poor outcome, favorable outcome, or non-significant) to each of the included studies for univariate and multivariate analyses as described in Section 2.4. Fig. 3 shows the distribution of reported outcomes associated with a high tumoral presence of CD163$^+$ cells in univariate and multivariate analyses. Results are shown for lung cancer, colorectal cancer, gastric cancer, liver cancer, breast cancer, and pooled for all five types of cancer.

Fig. 3a shows the distribution of outcomes associated with a high tumoral presence of CD163$^+$ cells in univariate analyses ($n = 155$). Most of the included studies (61%, $n = 95$) showed an association with poor outcome, with percentages ranging from 55% for colorectal cancer to 69% for gastric cancer. Thus, "poor outcome" was the most reported result for all types of cancer. In total, 9% ($n = 14$) of the included studies showed an association between high tumoral presence of CD163$^+$ cells and favorable outcome, with the highest rate for colorectal cancer (15%). In contrast, no studies of liver cancer showed association with favorable outcome. In addition, 30% ($n = 46$) of the included studies found no significant association between high tumoral presence of CD163$^+$ cells and patient outcome.

Fig. 3b shows the distribution of reported outcomes associated with a high tumoral presence of CD163$^+$ cells in multivariate analyses ($n = 78$). Consistent with the univariate analyses, most studies (64%, $n = 50$) showed an association with poor outcome, with percentages ranging from 56% for lung cancer to 83% percent for liver cancer.

In Figs. 3c and 3d, the distributions were calculated based on the number of patients in each study to ascribe more extensive studies more weight. For example, 22 lung cancer studies showed association with poor outcome in univariate analyses. These studies included 4198 patients, corresponding to 61% of the total number of included lung cancer patients across all studies performing univariate analyses ($n = 6881$). These distributions were similar to those shown in Figs. 3a and 3b, except for the reported multivariate results for lung cancer patients, where the studies reporting a poor outcome only accounted for 38% of the total number of included lung cancer patients (compared to 56% in Fig. 3b).

3.4. Histopathological localization

Macrophages are plastic cells [195], and TAMs in different localizations of the same tumor may develop distinct functions due to the specific local TME [11]. Some of the included reports have stated that they analyzed CD163 expression in specific histopathological localizations of the primary tumor or surrounding peritumoral tissue. Therefore, we next investigated whether the distribution of reported patient outcomes differed between various histopathological localizations. Here, the literature is inconsistent, and different studies used different terminology, even for the same type of cancer. However, after careful evaluation of the included studies, we decided to group the results into the following four categories of histopathological localizations: "Tumor epithelium" (tumor component encompassing tumor epithelial cells), "Tumor stroma" (tumor component describing the stromal areas between the areas of tumor epithelium), "Tumor periphery" (spatial localization including both invasive front, tumor margin/border, and peritumoral tissue), and "Tumor center" (spatial localization referring to areas of the tumor more central than the analyzed counterpart, e.g., invasive front). We have illustrated these different components/localizations in Fig. 4a using a section of formaldehyde-fixed paraffin-embedded breast cancer tissue stained with a monoclonal anti-human CD163 antibody (clone 10D6, 1:125, Novocastra, NCL-CD163). Details on the IHC procedure are shown in Sup. Fig. 2 along with a hematoxylin-eosin staining and two additional CD163 stainings using antibody clones MRQ-26 and EDHu-1. The three mentioned clones of anti-CD163 antibody were among the most commonly used in the included studies (Table 2). We used the three clones here to illustrate the different performances of these antibodies.

In terms of the association between CD163 expression in different histopathological localizations and reported patient outcome, we only included studies that clearly distinguished between different histopathological localizations by presenting results separately for e.g.

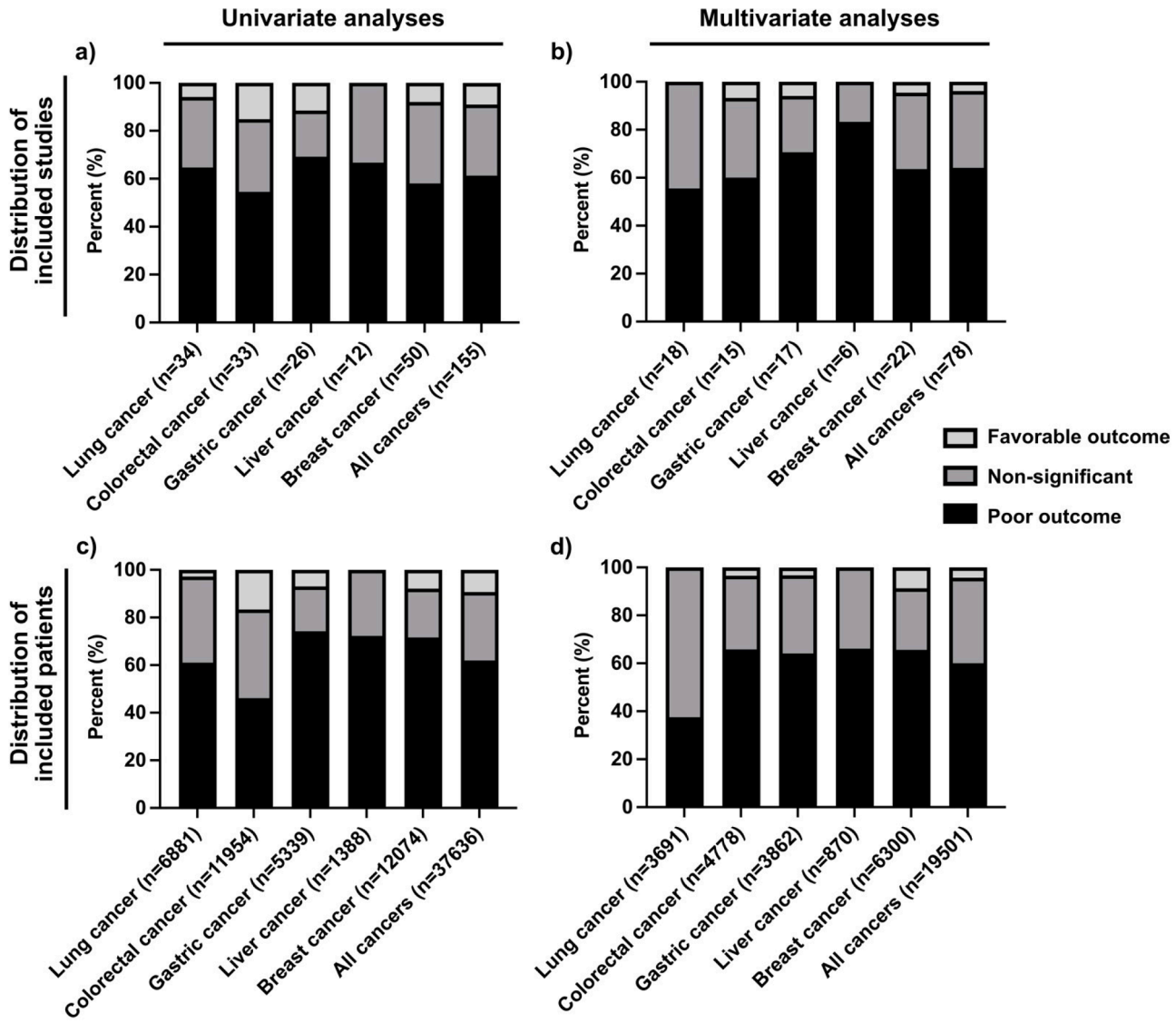

Fig. 3. Distribution of reported associations between high tumoral presence of CD163$^+$ cells and patient outcomes. A high tumoral presence either predicted a poor outcome, favorable outcome, or was not associated with outcome (non-significant). All studies were assigned to one of these categories based on their results from univariate and multivariate analyses as described in Section 2.4. a) and b) show the distribution of studies in the three categories for univariate and multivariate analyses, respectively. "n" indicates the number of included studies. c) and d) show the distribution of included patients in the three categories for univariate and multivariate analyses. "n" indicates the number of included patients.

"tumor center" and "invasive front" or by clearly defining the histopathological localization in which CD163 was measured. However, one study could contribute with more than one result to the grouped overview if they performed separate analyses for different histopathological localizations of the tumors. Only univariate analyses were considered. Analyses that combined CD163$^+$ cell counts from more than one of the four histopathological localizations were excluded unless it was possible to extract a clear result for one or more of the four specified categories. For transparency, details on the extracted data and how the different groups were constructed can be found in Sup. Tables 2, 3, and 4. Fifty-seven of the initial 157 included studies have contributed to the results in Figs. 4b and 4c. Due to the reduced number of studies, results are shown pooled for all five types of cancer.

Fig. 4b shows the distribution of reported associations between patient outcome and CD163$^+$ cell counts in the two spatial localizations "Tumor center" and "Tumor periphery", while Fig. 4c shows the distribution in the two tumor components "Tumor epithelium" and "Tumor stroma". It is seen that a high number of CD163$^+$ cells at the tumor periphery was most often reported to be associated with poor patient outcome. In contrast, many CD163$^+$ cells at the tumor center were most often reported not to be significantly associated with patient outcome. There were no apparent differences in the distribution of outcomes for tumor epithelium and tumor stroma. The distributions for each type of cancer can be seen in Sup. Table 4.

4. Discussion

Considering the heterogeneity of TAMs within the TME of human malignancies, evaluating the impact of different TAM subsets on patient outcomes may help to clarify which subsets to suppress or enhance with future anti-cancer immunotherapy. In the present review, we compiled current knowledge on the prognostic role of CD163$^+$ TAMs in five different types of solid tumors: Lung, colorectal, gastric, liver, and breast cancer. Our analyses showed that for all five types of cancer, a high tumoral presence of CD163$^+$ cells was most often associated with poor patient outcome in univariate analyses. This association was also found when calculating the distribution based on the number of patients included in the studies. The multivariate analyses showed similar

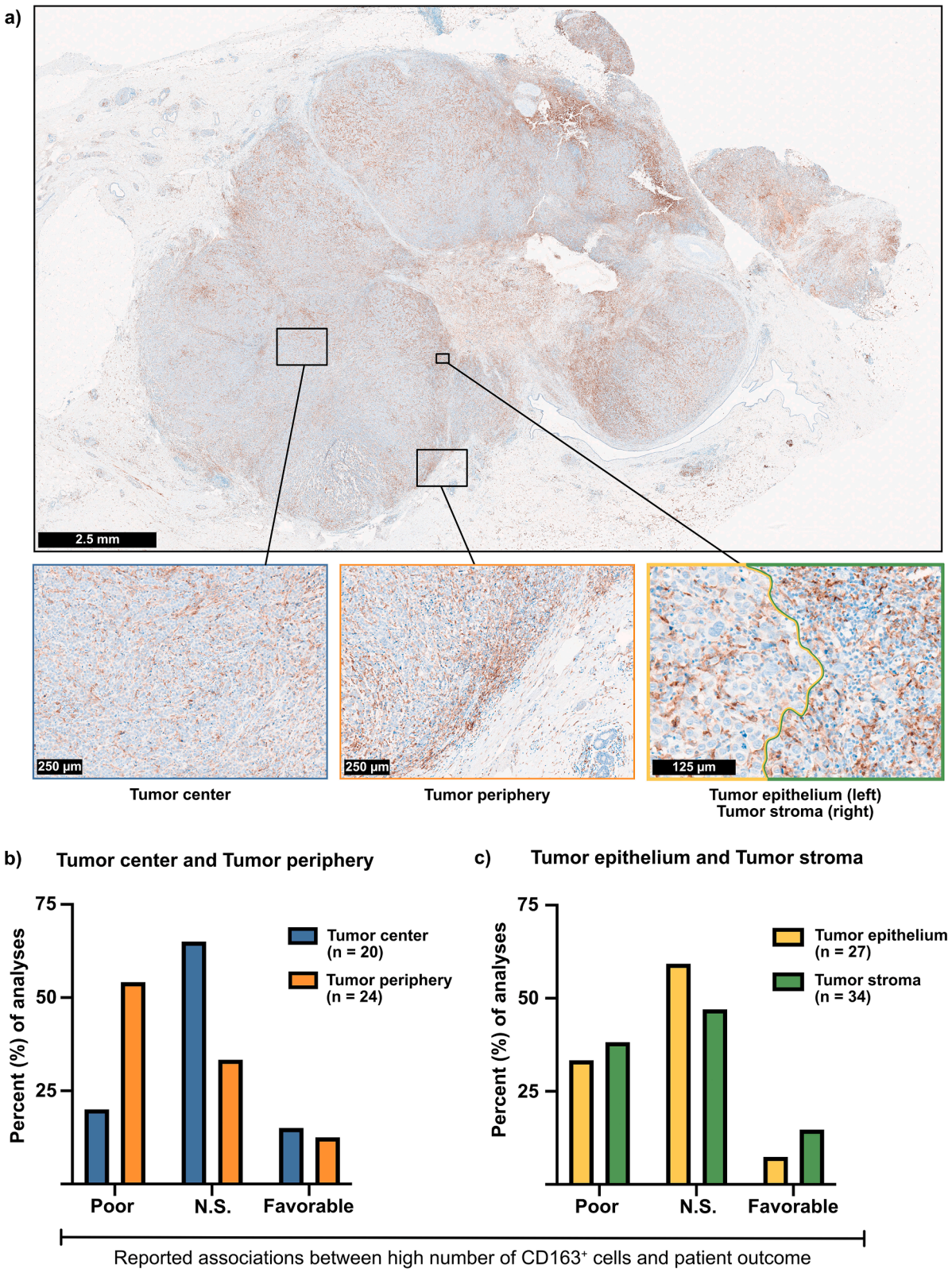

Fig. 4. **a)** Illustration of the different histopathological localizations used to group results in the present review: Tumor epithelium, Tumor stroma, Tumor center, and Tumor periphery. This example was made using a section of breast cancer tissue. CD163 was stained brown. **b + c)** Distribution of reported associations between a high number of $CD163^{+}$ cells and patient outcome in four different histopathological localizations: **b)** "Tumor center" and "Tumor periphery" and **c)** "Tumor epithelium" and "Tumor stroma". The results are shown pooled for all five types of cancer. "n" indicates the number of included analyses.

results, except for lung cancer, where a markedly higher percentage of studies found no significant association between high tumoral presence of CD163$^+$ cells and patient outcome. The distribution of reported associations from multivariate analyses must be considered to contain some bias, as most studies did not perform multivariate analyses when univariate analyses showed non-significant results. In general, it is also necessary to consider potential publication bias when interpreting these results, as studies finding no significant association between high tumoral presence of CD163$^+$ cells and patient outcome might be less likely to be published. Additionally, it is important to note that analytical variation may influence the results, since various antibodies and cut-offs have been used. This weakens the analytical validity due to risk of compromised reproducibility and reliability of the biomarker test.

Still, our findings are in agreement with previous systematic reviews and meta-analyses showing that a high tumoral presence of TAMs was associated with reduced patient survival [7,10,196–201]. On the contrary, in colorectal cancer patients, TAMs have also been associated with improved patient outcome in some meta-analyses [7–10]. However, many systematic reviews and meta-analyses evaluating the prognostic significance of TAMs are based on the tumoral presence of TAMs expressing the pan-macrophage marker CD68 or a mix of different markers [7–10,196–199,201]. Thus, these analyses may include TAM subsets with opposing functions in the TME, or even other cell types than TAMs [11]. Some reviews have attempted to distinguish between macrophage-subset markers (including CD163). However, the number of included studies in each group was often low ($\leq$3), making it difficult to draw any conclusions [9,199,200,202]. This lack was a strong argument for choosing the scoping review format for our present study, as we found it necessary to identify and map the body of literature regarding the prognostic value of CD163$^+$ TAMs specifically.

Our overview of reported results for different histopathological localizations indicated that the tumor periphery (including invasive front, tumor margin/border, and peritumoral tissue) may be most relevant for measuring CD163 expression compared to more central parts of the tumors in terms of predicting patient survival. The distribution of reported associations was very similar in the tumor stroma and tumor epithelium, which may reflect that it is less relevant to distinguish between these components when predicting patient survival or that the delineation of these components was often vague or differed between studies. For instance, in non-small-cell lung cancer, one study defined stromal macrophages as “macrophages in the area not occupied by tumor-cell-nests” [60], while another study described the stromal area as “the area where tumor stromal cells accounted for >70% of the total cells” [62].

In terms of histopathological localizations, our findings are subject to some uncertainty since many studies were excluded due to lacking information on where CD163 expression was measured. Therefore, we found it necessary to pool the results from the different cancers in the overview, and differences between cancer types may exist. Furthermore, the categorization of histopathological localizations may be associated with uncertainties due to interpretation, and the categorization itself is a simplification of a heterogenous collection of data, which is inevitably associated with a loss of nuances.

However, several studies across different types of cancer have reported that CD163$^+$ TAMs are especially dominating at the invasive front [77,101,163,165,203–205]. A study investigating the spatial heterogeneity of macrophages in gastric cancer patients by multiplex IHC identified seven major TAM subpopulations, five of which were considered to be M2-like TAMs based on CD163 and CD206 expression. They showed that CD68$^+$CD163$^+$CD206$^+$ macrophages accumulated at the tumor margin and decreased towards the tumor center. In contrast, the density of M1-like CD68$^+$IRF8$^+$ macrophages increased significantly from the margin to the center. Interestingly, after this finding, they stratified patients based on the TAM density in the tumor center (mainly containing M1-like TAMs) and found that higher density was associated with prolonged survival [206].

The previously mentioned study that identified a distinct population of tumor-promoting HO-1^{hi}CD163^{hi} TAMs also showed that this specific TAM subset accumulated at the invasive margin in both a mouse fibrosarcoma model and human metastatic melanoma lesions, which is consistent with pro-tumor functions such as promoting angiogenesis and metastasis formation [32]. The study that described the role of CD163$^+$ macrophages and HO-1 in driving resistance to vaccine-induced tumor regression also showed that this macrophage population primarily resided at the invasive tumor margin. Interestingly, this macrophage subset was not depleted by treatment with a CSF-1 inhibitor as opposed to macrophages residing inside the tumor. Some of the more central macrophages were also CD163$^+$, but they showed a dimmer expression of CD163 compared to the macrophages at the invasive margin [15]. This observation follows another study investigating the function of TAM subsets in a mouse melanoma model, where CD163^{hi} TAMs were found to accumulate at the tumor margin, while CD163^{low} TAMs were localized inside the tumor stroma [13]. Overall, results from the present review and the presented literature emphasize the importance of taking histopathological localization into account when analyzing the presence of TAM subsets in tumors.

Recently, a new aspect of macrophage heterogeneity has attracted significant attention, namely the ontogeny/origin of macrophages. Tumor-associated macrophages encompass both “tissue-resident macrophages” originating from the yolk sac and fetal liver, and “monocyte-derived macrophages” originating from the bone marrow [11]. While TAMs of different origins may have distinct transcriptional and functional profiles [11,207], subsets of both tissue-resident and monocyte-derived macrophages have been shown to exert tumor-promoting functions as reviewed in [207]. The CD163 receptor is known to be moderately expressed on circulating monocytes [18], but at the same time, pro-tumorigenic functions of specific CD163$^+$ tissue-resident macrophage subsets have been demonstrated in mouse models [14,15]. To our knowledge, it remains unknown whether CD163 is a marker of TAM origin, which should be investigated in future studies.

We conducted the present review to provide an overview of available literature regarding the association between a high tumoral presence of CD163$^+$ TAMs and patient outcome. Our results point towards CD163 being a potential marker of poor patient outcome, also supporting that the CD163$^+$ subset of TAMs may be an important future target for anticancer immunotherapy. A meta-analysis will be required to confirm that a high tumoral presence of CD163$^+$ TAMs in human tumors can function as a prognostic marker for reduced patient survival. Ideally, the prognostic value of CD163$^+$ TAMs should be investigated in more than the five types of cancer reviewed here to better understand the generalizability of the results across multiple tumor types. However, the remarkable heterogeneity of TAMs, which also seems to be associated with spatial TAM localization, makes it challenging to conduct a meta-analysis that considers both cancer type, specific macrophage markers, and histopathological localizations. Furthermore, single markers might be insufficient to identify tumor-promoting TAM subsets in the complex TME. Different omics technologies, including spatial omics, are becoming widely available tools to investigate TAM heterogeneity in tumors. While these technologies can provide valuable insight into the complex TAM compartment, they might further complicate the preparation of systematic reviews and meta-analyses in this field [11,208].

In conclusion, a high number of CD163$^+$ TAMs in tumors, especially at the tumor periphery, may be predictable for a poor patient outcome. This should be investigated further in future studies, also taking the spatial localization of CD163$^+$ TAMs into consideration. Such studies may pave the way for targeted immunotherapy aiming to deplete or reprogram tumor-promoting CD163$^+$ TAMs to improve patient outcome.

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Ethical statement

The tissue used for CD163 staining as shown in Fig. 4 was from a patient included in a previous study focused on examining the tumor microenvironment in breast cancer. This study was approved by the local ethics committee (1–16–02–698–17).

Data availability statement

This paper is a review based on already published literature. All included studies can be found on the reference list. Any additional information required to reanalyze the data reported in this paper is available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Henriette Mathiesen: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Funding acquisition, Conceptualization. **Kristian Juul-Madsen:** Writing – review & editing, Methodology, Investigation, Funding acquisition. **Trine Tramm:** Writing – review & editing, Supervision, Resources, Methodology. **Thomas Vorup-Jensen:** Writing – review & editing, Supervision. **Holger Jon Møller:** Writing – review & editing, Supervision. **Anders Etzerodt:** Writing – review & editing, Supervision. **Morten Nørgaard Andersen:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Resources, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

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