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# Alpha 5 integrin as a prognostic biomarker for survival in carcinomas: a systematic review

Natalie Ap. Rodrigues Fernandes[1,2], Milena Moraes de Carvalho[1], Lélio Fernando Ferreira Soares[1], Wafa Wahbi[2], Tuula Salo[2,3], Ahmed Al-Samadi[2,4] and Carlos Rossa Junior[1*]

*Correspondence:
Carlos Rossa Junior
c.rossa@unesp.br
[1]Department of Diagnosis and Surgery, School of Dentistry, São Paulo State University (UNESP), Rua Humaitá, 1680 – Centro, Araraquara, SP 14801-903, Brazil
[2]Department of Oral and Maxillofacial Diseases, Clinicum, Faculty of Medicine, University of Helsinki, Helsinki, Finland
[3]Medical Research Center, Oulu University Hospital, Oulu, Finland
[4]Institute of Dentistry, School of Medicine, University of Eastern Finland, Kuopio, Finland

**Abstract**

Altered integrin expression in carcinomas has been associated with tumor aggressiveness, including survival outcomes. The alpha 5 (α5) integrin is associated with increased proliferation, invasion, migration, and metastasis in various types of cancer, however there is no systematic review on its potential as a prognostic marker for survival outcomes. This systematic review analyzed studies reporting α5 integrin detection by immunohistochemistry and associated survival outcomes, retrieved from PubMed, Embase, Scopus, and the Cochrane Library databases. Fourteen publications met the inclusion criteria including a total of 2,018 patients diagnosed with ovarian, colorectal, liver, cervical, esophageal, pancreatic ductal, tongue or bladder carcinoma. The survival outcomes assessed in these studies included overall survival (OS), progression-free survival (PFS), recurrence-free survival (RFS), and percent survival. Eleven studies reported a positive association between elevated α5 integrin expression and poorer OS or percent survival, while two found no association. Reduced PFS was associated with elevated α5 integrin expression in three studies, whereas two studies reported no such association. One study evaluated α5 integrin expression in relation to RFS and found no association. In conclusion, there is evidence that increased α5 integrin expression is associated with poorer overall and progression-free survival in carcinomas. However, these findings should be further validated through additional research to confirm its potential as a prognostic marker.

**Keywords** Carcinoma, Prognosis, Alpha 5 integrin, Survival

## 1 Introduction

Carcinomas are neoplasms of epithelial tissues that account for approximately 90% of all cancer cases in the world [1], with a global incidence of close to 17 million new cases and 9 million deaths from cancer annually [1]. Invasion and metastasis account for the majority of cancer-related deaths, and are largely driven by interactions between cancer cells, stromal cells, and components of the extracellular matrix [2].

Integrins are the main cell membrane receptors interacting with components of the extracellular matrix and play critical roles in cancer [3]. Integrins are composed of heterodimers of α and β subunits with transmembrane domains. Eighteen α and eight β

subunits have been described in humans [4]. The alpha 5 (α5) integrin forms a heterodimer exclusively with the beta 1 (β1) integrin, known as the α5β1 integrin, and changes in its expression have been reported in many human cancers [5]. The α5 integrin has an essential role in the proliferation, differentiation, and survival of different cell types under physiological conditions [6–8] and aberrant integrin signaling induces oncogenic changes [3, 9].

Tumor growth and invasion are not solely the result of malignant transformation of epithelial cells; they are also influenced by the surrounding tumor stroma [10]. Variations in the prevalence of non-neoplastic cells that express α5 integrin may indirectly affect tumor progression and response to treatment [11]. For example, α5β1 integrin is highly expressed in endothelial cells and plays a key role in tumor angiogenesis. Preclinical studies have supported targeting α5β1 as an anti-angiogenic strategy for cancer treatment [12]. However, phase I and II clinical trials using antibodies that target α5β1 integrin have shown limited success [13–15]. It is important also to note that these clinical trials were based on preclinical research that primarily assessed the effect of α5β1 integrin on angiogenesis [16, 17], rather than other biological effects [5]. Also, the clinical trials focused on tumor size as the primary endpoint for therapeutic efficacy. One limitation of this approach is that it does not account for other critical factors, such as changes in tumor biology, tumor heterogeneity, or survival outcomes. In addition, the composition of the extracellular matrix (ECM) plays a significant role in modulating malignant behavior [10]. Fibronectin, a glycoprotein in the ECM, interacts with α5β1 integrin to directly activate c-Met, a tyrosine kinase receptor and proto-oncogene [18]. Indeed, increased expression and signaling through α5β1 integrin in different cells of the tumor microenvironment have been linked to enhanced proliferation, invasion, migration, and metastasis in several cancers [5, 19–21].

Despite the limited results of clinical trials, the prognostic value of the α5β1 integrin in survival outcomes of carcinomas patients remains inconclusive, and no systematic review is available to date. In this review, we focused on immunohistochemistry-detected expression of α5 integrin because this is a commonly-used technique that may be readily performed in paraffin-embedded sections of biopsies and surgical specimens, aggregating valuable prognostic information that may be used to customize both treatment and follow-up of carcinoma patients. Therefore, we performed a systematic review to investigate the significance of α5 integrin expression as a prognostic biomarker for survival in carcinoma patients.

## 2 Materials and methods

### 2.1 Protocol registration and focused review question

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [22] and registered at the International Prospective Register of Systematic Reviews PROSPERO under registration number CRD42024505960.

We established our research question according to the Population, Variables, and Outcomes (PVO) strategy: (i) Population: patients with carcinoma; (ii) Variable: α5 integrin expression detected by immunohistochemistry (IHC); (iii) Outcome: survival analysis. The focused review question was: "What is the prognostic value of integrin α5 in predicting survival outcomes of carcinomas?".

### 2.2 Inclusion and exclusion criteria

Inclusion criteria for study selection were: clinical studies reporting the association between expression of α5 integrin detected by IHC in carcinoma tissues and patient survival. We excluded studies not published in English, erratas, book references, letters, case reports, commentaries, conference papers, reviews, in vitro and pre-clinical in vivo (animal) studies.

### 2.3 Search strategy

We carried out a systematic and comprehensive search in PubMed, Embase, Scopus, and Cochrane Library databases up to January 24, 2024. The search strategies were formulated using Medical Subject Headings (MeSH) or Embase Subject Headings (Emtree) terms related to α5 integrin and carcinomas, with syntax adjustments applied across the databases (Table S1, available in the ESM_1 file). Unpublished manuscripts and grey literature were not searched, and a filter for humans was not applied, but it was considered in the manual study selection.

The literature search in all electronic databases was exported to Rayyan [23] in order to organize, manage, and eliminate duplicate references. Two investigators (NARF and MMC) independently performed the initial search for assessment of titles and abstracts, according to the inclusion/exclusion criteria and the search results were checked for agreement. The full text of studies that met the eligibility criteria were read and the data was extracted using a standardized table made in Microsoft Excel.

### 2.4 Data extraction

The following data was extracted: (i) manuscript information including publication year, study period, follow-up duration, and the first author; (ii) case cohort information including age, gender, country, and total case number; (ii) tumor information including disease stage and tumor site; (iii) outcome measures, such as survival data, Kaplan–Meier curves, recurrence, statistical results (estimated hazard ratio [HR], 95% confidence interval [CI], and p-values) and number of events; (iv) other variables including methods for quantitative immunohistochemical integrin expression.

### 2.5 Quality assessment

Two review authors (NARF and MMC) independently assessed the risk of bias answering 10 questions for each study using The Joanna Briggs Institute Model for Evidence-Based Healthcare (JBI) critical appraisal tool [24]. Answers were described as Y for "yes," N for "no," U for "unclear," and NA for "not applicable". The risk of bias was categorized as high when the study had a "yes" score of 49% or less, moderate when the "yes" score was between 50% and 69%, and low when the study had a "yes" score of 70% or more. For resolving conflicting evaluations, an agreement was reached following bias assessment evaluation with a third investigator (WW).

## 3 Results

### 3.1 Study selection

The initial search retrieved a total of 2,176 potentially relevant studies from the electronic databases. After removing duplicates, 1,660 studies remained. Titles and abstracts were then screened based on the predefined inclusion and exclusion criteria, resulting in

63 articles for full-text reading. Ultimately, 14 articles [11, 25–37] met the inclusion criteria and were included for data extraction and quality assessment. A flowchart detailing the inclusion and exclusion processes is presented in Fig. 1.

### 3.2 General study characteristics

The selected studies, published between 2008 and 2023, included a total of 2,018 patients diagnosed with carcinoma, with the number of patients per study ranging from 30 to 355. These studies assessed α5 integrin expression in carcinoma tissues using IHC and examined its association with survival outcomes. The research was conducted across six countries: the United States, Japan, China, the Netherlands, Germany, and Egypt.

The tumor sites represented in the studies were ovarian [25–27, 31–33], bladder [30], esophageal [34], tongue [35], pancreatic ductal [36], colorectal [11, 37], liver [28], and cervical [29]. One study [36] did not report the gender of the subjects, while seven studies (ovarian and cervical cancers) included only women, and the remaining six studies had a majority of male participants. With the exception of one study [31], age of the participants was always reported. Two studies did not specify the disease stage classification used [31, 35].

Regarding the methods for quantitative immunohistochemistry assessment of the α5 integrin expression, most studies employed well-defined quantification methods and cut-off points, with independent assessment by at least two examiners. However, the cut-off points for α5 expression varied among studies, which may represent a limitation of this systematic review due to the potential differences in expression levels considered for association with the outcomes. Still, all studies included at least a "positive" classification for α5 expression which was compared to either a "negative" or "low" expression group. This limitation does not impair the main goal of this systematic review, which is to evaluate the prognostic significance of α5 expression in the survival outcomes of carcinoma patients. Additionally, four studies did not specify the cut-off point for α5 expression [11, 26, 35, 37].

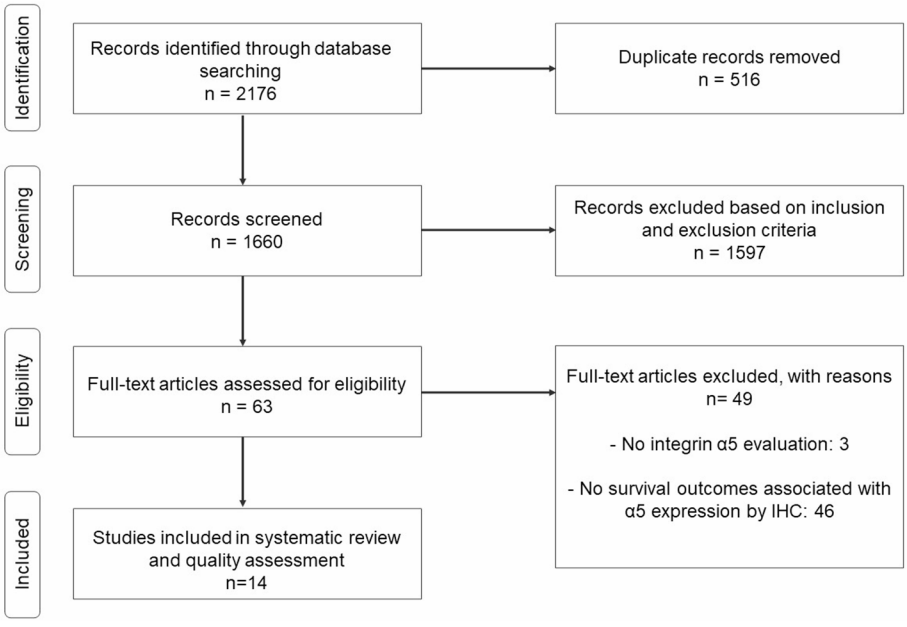


**Fig. 1** Flow chart used in this systematic review, adapted from PRISMA [22]

The selected articles employed Kaplan-Meier, univariate, and/or multivariate analyses to investigate α5 expression (determined by IHC) in tumor tissues as a prognostic marker for survival outcomes. The survival outcomes evaluated in the studies included Overall Survival (OS), Progression-Free Survival (PFS), Recurrence-Free Survival (RFS), and percent survival. The main features and findings of the studies are presented in Table 1, as well as in Supplementary Tables S2, S3, S4, and S5, which are included in the ESM_1 file.

### 3.3 Survival analysis

OS (Table S2): Twelve studies evaluated the association between α5 expression and OS [11, 25–29, 31–34, 36, 37]. 'Positive', 'high', or 'overexpression' of α5 has been associated with reduced OS in ovarian [25, 26, 32, 33], colorectal [11, 37], liver [28], cervical [29], esophageal [34] and pancreatic ductal [36] carcinoma. In ovarian carcinoma, studies were conducted in four different countries: United States [25], China [26, 33], Japan [32] and Germany [27]. The disease stages evaluated varied across studies, including FIGO stages II-IV [25], III [32] and I-V [26, 33]. However, two studies did not find an association between α5 expression and OS in ovarian cancer for early I-II [32] and advanced IIIb-IV [27] stages. α5 expression was also identified as an independent risk factor for decreased OS in some studies [31, 33]. For colorectal carcinoma [11, 37], the studies were conducted in China and included patients with TNM stages 0-IV. In liver [28], pancreatic ductal [36], and cervical [29] carcinomas, the patient cohorts included TNM stages I–III, I–III, and FIGO stages IA1–IIA2, respectively. In esophageal carcinoma [34], the disease stage was not specified. In colorectal, cervical, esophageal, and pancreatic cancers, increased α5 expression was also identified as an independent risk factor for decreased OS.

PFS (Table S3): Five studies reported the association between α5 expression and PFS in colorectal [11] and ovarian [25, 27, 32, 33] carcinomas. In three studies [25, 27, 33], patients underwent surgical resection of the tumor followed by chemotherapy. One study [32] reported only tumor resection, and another study [11] treatment included tumor resection and immunotherapy (programmed cell death ligand 1 PD-L1 blockade). 'Positive', 'high', or 'overexpression' of α5 was associated with reduced PFS [25, 32, 33] in three of these five studies. Two studies found no association between α5 expression and PFS [11, 27]. High α5 expression was identified as a significant variable for decreased PFS in the univariate analysis of one study [33]. However, when accounting for the effects of other selected variables in the multivariate regression model, it was not found to be significant for PFS in the same study [33].

RFS (Table S4): One study assessed RFS [30] and did not find association between α5 expression and the length of time from the date of the transurethral resection to the first intravesical recurrence in bladder carcinoma. The median follow-up period was 47 months (range: 13–93 months), and strong α5 expression was defined as staining in more than 50% of the cells.

Percent survival (Table S5): One study [35] evaluated tongue cancer and assessed the percentage of survival in patients with 'high' and 'low' α5 expression, finding a positive association between high α5 expression and reduced percent survival.

**Table 1** General characteristics of the studies included in this review

| First author | Year | Country | Tumor site | Method for IHC evaluation | Cut-off point | Survival outcomes | Results interpretation |
|---|---|---|---|---|---|---|---|
| Sawada et al. [25] | 2008 | USA | Ovarian | Percentage of positive cells (0, ≤ 10%; 1, 10–25%; 2, 25–50%; 3, ≥ 50%) and the intensity of the staining (0, none; 1, weak; 2, strong) | Overexpression of α5 – Strong staining (intensity 2) in ≥ 50% of tumor cells (score 3) | OS and PFS | Overexpression of α5 is associated with reduced OS and PFS |
| Behnsawy et al. [30] | 2011 | Japan | Bladder | Five staining levels (0, no staining; 1, 1–25%; 2, 25–50%; 3, 50–75%; and 4, 75–100%) | Strong expression if more than 50% of cells expressed the antigen (staining levels 3 and 4) | RFS | Strong expression of α5 is not associated with RFS and is not considered a risk factor affecting RFS |
| Hu et al. [31] | 2012 | China | Ovarian | Intensity (0, no pigmentation; 1, light yellow; 2, buff; and 3, brown) and percentage of positive staining (0, less than 5%; 1, 5–25%; 2, 26–50%; 3, 51–75%; 4, greater than 75%) | Score ≥ 3 (intensity x percentage) was considered positive expression | OS | α5 positive expression is an independent risk factor that reduces OS |
| Ohyagi-Hara et al. [32] | 2013 | Japan | Ovarian | Percentage of positive cells (0, <= 10%; 1, 10–25%; 2, 25–50%; and 3, >=50%) and the intensity of the staining (0, none; 1, very weak; 2, weak; and 3, strong) | Score ≥ 5 (intensity x percentage) was considered high expression | OS and PFS | High expression of α5 is associated with reduced OS and PFS in advanced disease stage, but not in early stages |
| Zhu et al. [33] | 2015 | China | Ovarian | Estimated percentage and average intensity of tumor cells that stained positive. A final score (0-300) was determined by multiplying percentage score and intensity score | The median value of all scores was chosen as the cutoff point for low and high expression | OS and PFS | High expression of α5 is associated with reduced OS and PFS and is an independent risk factor for decreased OS |

**Table 1** (continued)

| First author | Year | Country | Tumor site | Method for IHC evaluation | Cut-off point | Survival outcomes | Results interpretation |
|---|---|---|---|---|---|---|---|
| Xie et al. [34] | 2016 | China | Esophageal | Immunostaining intensity (0, no staining; 1, weak staining; 2, moderate staining; 3, strong staining) and the percentage of positive cells (0, < 5%; 1, 5%-25%; 2, 26%-50%; 3, 51%-75%; and 4, > 75%) | Score ≥ 5 (intensity x percentage) was considered high expression | OS | High expression of α5 is associated with reduced OS |
| Deng et al. [35] | 2019 | China | Tongue | Low, Moderate and high expression | - | Percent survival | α5 high expression is associated with worse survival |
| Kuninty et al. [36] | 2019 | Netherlands | Pancreatic ductal | Percentage of stained cells (0, absence; 1, < 25%; 2, 26 to 50%; and 3, > 50%) and staining intensities (1, mild; 2, moderate; and 3, intense | Score > 4 (intensity x percentage) was considered positive expression | OS | Positive expression of α5 is associated with reduced OS and is an independent risk factor for decreased OS |
| Lu et al. [37] | 2019 | China | Colorectal | H score = Σ(I 9 Pi) = (percentage of cells of weak intensity x 1) + (percentage of cells of moderate intensity x 2) + (percentage of cells of strong intensity x 3), where I = intensity of staining and Pi = percentage of stained tumor cells, producing scores ranging from 0 to 300 | - | OS | High expression of α5 is associated with reduced OS and is an independent risk factor for decreased OS |

**Table 1** (continued)

| First author | Year | Country | Tumor site | Method for IHC evaluation | Cut-off point | Survival outcomes | Results interpretation |
|---|---|---|---|---|---|---|---|
| Li et al. [26] | 2020 | China | Ovarian | Staining percentage (1, 1–25%; 2, 26–50%; 3, 51–75%; or 4, 76–100%) and staining intensity (0, negative; 1, weak; 2, moderate; or 3, strong). | - | OS | High expression of α5 is associated with reduced OS |
| Krajnak et al. [27] | 2022 | Germany | Ovarian | Intensity of immunostaining (0, negative; 1, weak; 2, moderate; 3, strong) and the area of positive staining (0, negative; 1, 1–10%; 2, 11–50%; 3, 51–80%; 4, 80–100%). | Score ≥ 1 (intensity x percentage) was considered positive expression | OS and PFS | α5 expression is not associated with OS and PFS |
| Helal et al. [28] | 2022 | Egypt | Liver | 1 (no staining), 2 (fewer than 15% positive staining), 3 (15% – 50% positive cells), 4 (more than 50% positive cells). | 3 and 4 were grouped as positive | OS | α5 positive expression is associated with reduced OS |
| Lu et al. [11] | 2023 | China | Colorectal | H score, ranging from 0 to 300 | - | OS and PFS | Positive staining of α5 is associated with reduced OS and is a risk factor for decreased OS; positive staining is not associated PSF |
| Xu et al. [29] | 2023 | China | Cervical | Staining intensity (0, none; 1, week; 2, moderate; 3, strong) and staining area (0, < 5%; 1, < 25%; 2, 25%~50%; 3, 51%~75%; 4, > 75%) | Score > 6 (median) was considered high expression | OS | High expression of α5 is associated with reduced OS |

### 3.4 Risk of bias

Based on the JBI evaluation tool, the risk of bias in the included articles was low in 13 articles and high in one article. The risk of bias for each study and the evaluation criteria are shown in Table S6, available in the ESM_1 file.

## 4 Discussion

Carcinomas develop from neoplastic transformation of epithelial cells within a microenvironment in which these cells usually express various integrins, which interact with diverse extracellular matrix components [38–40]. Integrins have an essential role in the acquisition of an aggressive phenotype by cancer cells, as they can influence processes such as migration and invasion [38, 41]. Consequently, it is conceivable that altered integrin expression in carcinomas may be associated with tumor aggressiveness, including survival outcomes, and therefore could be of prognostic value. Although several studies have reported an association between α5 integrin expression and survival outcomes in carcinomas, no systematic review has yet evaluated the prognostic significance of α5 integrin. This systematic review addresses that gap by including 14 eligible studies involving a total of 2,018 patients for qualitative analysis.

The α5 integrin can influence proliferation, migration, invasion, and epithelial-mesenchymal transition (EMT) phenotype of carcinoma cells [18, 35, 42]. Its involvement in these processes highlights its significance in cancer biology, making it both an attractive therapeutic target and a potential prognostic marker of tumor aggressiveness. A qualitative assessment of twelve reviewed studies demonstrated that positive, high or overexpression of α5 was associated with reduced OS in ovarian [25, 26, 32, 33], colorectal [11, 37], liver [28], cervical [29], esophageal [34], pancreatic ductal [36] and tongue [35] carcinomas. Moreover, α5 expression was identified as an independent risk factor for poorer OS in ovarian carcinomas in two studies [31, 33]. Despite the heterogeneity across the studies, including for example differences in tumor site, patient population, tumor stage and the methods used for IHC evaluation and cut-off determination, there is evidence that α5 integrin expression in carcinoma tissues is associated with poorer OS. However, two studies reported no association between α5 integrin expression and OS in ovarian cancer [27, 32]. These differences in findings may be attributed to the stratification of FIGO stages used in their analyses (IIIb-IV [27] and I-II [32]), which was not performed in the other ovarian carcinomas studies that analyzed broader stage ranges (stages I-IV or II-IV [25, 26, 31, 33], except for one that focused on stage III [32]), . Additionally, differences in extracellular matrix composition and variations in the relative prevalence of α5-expressing cells may directly or indirectly affect tumor progression and treatment response [11, 43–45].

Preclinical studies have demonstrated that α5 integrin expression and signaling are involved in treatment resistance in carcinomas [46–49]. In this systematic review, three studies involving ovarian carcinoma cohort [25, 32, 33] assessed PFS and found that positive, high or overexpression of α5 integrin was associated with reduced PFS. In contrast, two studies, one in ovarian [27] and other in colorectal [11] carcinomas, did not find any association. All ovarian cancer studies included patients who underwent surgical resection or cytoreductive surgery followed by adjuvant chemotherapy, except for one study [32] in which patients received only primary debulking surgery. Notably, the ovarian cancer study that did not find an association included patients in FIGO stage IIIb–IV [27], suggesting that in more advanced stages, α5 integrin expression may not be associated with PFS in patients receiving standard ovarian cancer treatment. Additionally, one study [30] reported no association between α5 expression and RFS in patients diagnosed with non-muscle-invasive bladder carcinoma (TNM stage Ta or T1) who were treated

with transurethral resection and intravesical BCG therapy. In this study, α5 was not identified as an independent risk factor for RFS in bladder cancer.

The limitations of this study include: (i) clinical heterogeneity across studies, including differences in tumor site, stage (and classification), follow-up periods, sample size and treatment regimens; (ii) antibodies supplied by different companies, including detection of different epitopes; (iii) labeling conditions (such as processing/fixation, antigen retrieval, blocking, etc.), which could result in variations in staining results; (iv) intrinsic IHC limitations, such as background intensity, false-positive results, and the multi-step procedure leading to variability; (v) different quantitation approaches and cutoff points used to determine α5 expression.

In conclusion, this systematic review indicates that α5 integrin expression is a prognostic factor associated with increased aggressiveness in carcinomas. Despite the considerable heterogeneity among the included studies, there is evidence that positive, high, or overexpression of α5 integrin is associated with poorer OS across different carcinoma types, as well as with reduced PFS in ovarian carcinoma. These findings should be further validated through studies that establish standardized tumor grading for comparison, define a consistent method and cut-off score for IHC-based quantification of α5 expression, and include a broader range of carcinoma types to strengthen the quality of the evidence.

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s12672-025-03530-y.

Supplementary Material 1.

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**Author contributions**

NARF: Conceptualization; investigation; writing—original draft; writing—review and editing. MMC: conceptualization; investigation; writing—review. LFFS: investigation; writing—review. WW: investigation; writing—review. TS: conceptualization and review. AAS: conceptualization and review. CRJ: conceptualization; review and editing.

**Data availability**

No datasets were generated or analysed during the current study.

## Declarations

**Ethics approval and consent to participate**

This manuscript is a systematic review article and does not require approval by an ethics committee.

**Consent for publication**

Not applicable.

**Competing interests**

Non-financial competing interest statement: Ahmed Al-Samadi is an Editorial Board Member of Discover Oncology, but he was not involved in the handling or decision-making process related to this submission.

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