

Use of Anti-transcriptional Intermediary Factor-1 Gamma Autoantibody in Identifying Adult Dermatomyositis Patients with Cancer: A Systematic Review and Meta-analysis

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Anti-transcriptional intermediary factor-1 γ (TIF-1 γ) autoantibody may be associated with cancer in adult patients with dermatomyositis. The aim of this study was to evaluate the risk of cancer in the presence of anti-TIF-1 γ autoantibody in adult dermatomyositis. A comprehensive database search of EMBASE, MEDLINE and the Cochrane Library up to May 2018 was performed using the main key words "dermatomyositis", "myositis", "inflammatory myopathies" and "anti-TIF-1". Eighteen studies, with a total of 1,962 dermatomyositides, were included in the meta-analysis. The pooled prevalence of cancer-associated dermatomyositis in patients with anti-TIF-1 γ autoantibody was 0.41 (95% confidence interval (CI) 0.36–0.45). In the presence of anti-TIF-1 γ autoantibody, the overall diagnostic odds ratio of cancer was 9.37 (95% CI 5.37–16.34) with low heterogeneity (Cochran's Q: 14.88 (df = 17, $p = 0.604$); $I^2 = 0\%$). The results of this systematic review confirm that detection of anti-TIF-1 γ autoantibody is a valuable tool to identify a subset of adult dermatomyositis patients with higher risk of cancer.

Key words: anti-transcriptional intermediary factor-1 γ autoantibody; cancer; dermatomyositis; meta-analysis.

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The risk of cancer in adults with dermatomyositis (DM) has been reported extensively in the literature (1–6). Various clinical findings and laboratory markers, including tumour markers, muscle enzymes and myositis-specific autoantibodies (MSA), have been studied to screen and identify adult patients with DM at risk for cancer (7–12). Anti-transcriptional intermediary factor-1 γ (TIF-1 γ) autoantibody was identified in 2006 by Targoff et al. (13) as a novel autoantibody directed against a 155-kDa protein in a large series of myositides. Initially referred to as anti-p155, the autoantigen was then identified as a member of the TIF-1 gene family involved in transforming the growth factor

SIGNIFICANCE

The risk of cancer in adults with dermatomyositis has been reported extensively in the literature, with a global malignancy rate ranging from 6.7% to 32%. Identifying adult patients with dermatomyositis at high risk for cancer is a challenge for clinicians. In this systematic review and meta-analysis of all relevant published studies the myositis-specific autoantibody anti-Tif1 γ has been confirmed to be a valuable tool to identify a subset of adult DM patients with higher risk (9.37 fold) of cancer.

(TGF)- β) signalling pathway (14, 15). The relationship between anti-TIF-1 γ autoantibody and cancer-associated DM (CAD) was first noted in a series of 45 adult DM with an odds ratio (OR) for CAD in the presence of anti-TIF-1 γ autoantibody of 48.18 (95% confidence intervals (95% CI): 2.46–943.31) (13). Multiple cohort studies (16–35) then continued to investigate the risk of CAD in the presence of anti-TIF-1 γ autoantibody, but mostly in limited series. Two meta-analyses performed on 6 (312 patients) (13, 16–20) and 8 (408 patients) (13, 16–21, 25) cohort studies, respectively, found a pooled OR for CAD of 27.26 (95% CI 6.59–118.82) (36) and a relative risk (RR) for CAD of 5.57 (95% CI 2.91–10.65) in the presence of anti-TIF-1 γ autoantibody (12). Since then, numerous large studies (24, 26–29, 31, 32, 34, 35) with cohort series of up to 376 patients (24) have been published, sometimes showing a less pronounced association between anti-TIF-1 γ autoantibody and cancer (27, 28, 34).

Therefore, to better assess the relationship between anti-TIF-1 γ autoantibody and cancer in adults with DM, a systematic review and meta-analysis of all relevant published studies was performed.

MATERIALS AND METHODS

Search strategy

The main investigators (MB and DB) searched EMBASE, MEDLINE and the Cochrane Database of Systematic Reviews up to December 2017 with update for original articles up to May 2018. Searches were restricted to articles written in English. The search

strategy combined free-text search, exploded Medical Subject Headings (MeSH)/Emtree terms and all synonyms of the following MeSH terms: “dermatomyositis”, “myositis”, “inflammatory myopathies” and “anti-TIF-1” (see detailed search strategy in Appendix S1¹). We also searched for additional references from the reference lists of relevant papers obtained from the electronic search with a large equation using the combination of MeSH terms “dermatomyositis” and “antibody”. We adapted the search strategy to the special features of each database.

Study selection

Observational studies were considered if they assessed the sensitivity and specificity of anti-TIF-1 autoantibody for the diagnosis of CAD and if they met the following criteria: (i) original data reported with no restrictions on the study design; (ii) adult patients or a majority of adult patients with a median age in the cohort > 50 years included, with “probable” or “definite” DM according to Bohan & Peter’s criteria (37, 38) or amyopathic DM according to Sontheimer’s (39) or Gerami et al’s (40) criteria; (iii) more than 20 patients included; (iv) anti-TIF-1 γ autoantibody determined by immunoprecipitation (IP) assay, enzyme-linked immunosorbent assay (ELISA), immunoblot (IB) assay or immunodot assay; (v) the number of patients with cancer among the participants reported (diagnosed according to each author’s criteria); and (vi) sufficient information included to calculate diagnostic odds ratios (DOR) with 95% CI. Reviews, editorials, guidelines and case reports were excluded (Fig. 1). If data were duplicated in more than one study, the more complete study was included. Risk of bias and applicability concerns were assessed by adopting the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool (41).

Data extraction

Two investigators (MB and DB) independently reviewed each retrieved article. Disagreement between the 2 reviewers was resolved by discussion and consensus of all co-authors. The senior investigator (DB) confirmed the final results. The information recorded for each selected study included the study design, the inclusion criteria and period of inclusion, and patient characteristics, including mean age at diagnosis, follow-up duration, number of patients positive for anti-TIF-1 γ autoantibody, number of CAD in the cohort, number of CAD with a positive result for anti-TIF-1 γ autoantibody, and detailed information about cancer, if available. Concurrently, data regarding the methods used to identify anti-TIF-1 γ autoantibody and the criteria to define CAD were also extracted.

Study level analysis and meta-analytic model

The diagnostic performance (i.e. sensitivity, specificity and corresponding 95% CI) was recalculated for each primary study from these data. A bivariate random-effect model developed for meta-analysis of diagnostic accuracy studies was applied, as recommended by the Cochrane collaboration (42–44). In this model, the logit transforms of the true sensitivity and true specificity in each study are assumed to have a bivariate normal distribution across studies, thereby allowing for the possibility of correlations between them. We used the mada package in the R statistical software to calculate summary sensitivity and specificity values based on the inverse logit transform of the estimated model parameters, while assuming their estimates have a normal distribution. Corresponding positive and negative likelihood ratios (LRs), diagnostic

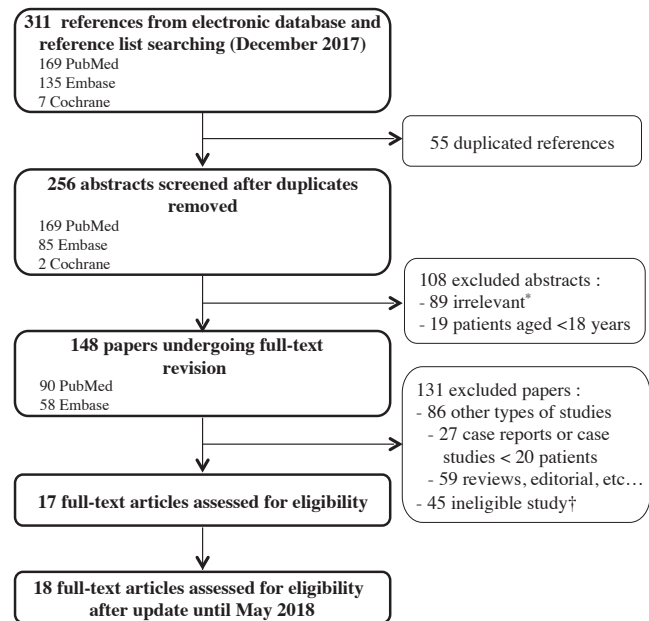


Fig. 1. Flow-chart for study selection. *Abstracts were considered irrelevant due to: (i) absence of dermatomyositis (DM) or inflammatory myositis studies (IM); (ii) studies limited to DM or IM treatments; (iii) studies limited to immunological assay for myositis-specific autoantibody (MSA); (iv) studies limited to MSA other than anti-transcriptional intermediary factor-1 γ (anti-TIF-1 γ) autoantibody; and (v) *in vitro* studies. †Studies not meeting the criteria for inclusion: studies restricted to: (i) clinically amyopathic DM; (ii) patients with positive myositis-specific autoantibody; or (iii) patients with cancer or interstitial lung disease; studies about IM without details on the subgroup of DM; studies without evaluation of cancer or autoantibody; studies with < 20 DM.

log odds ratios, and their corresponding 95% CI were derived as functions of these summary estimates. The following interpretations could be applied to positive LR and negative LR: positive LR greater than 10 and negative LR of less than 0.1 implied large changes; positive LR of 5–10 and negative LR of 0.1–0.2 implied moderate changes; positive LR of 2–5 and negative LR of 0.2–0.5 implied small changes; positive LR of less than 2 and negative LR greater than 0.5 implied tiny changes; and LR of 1 implied no change (43). We delimited the 95% confidence ellipse around the mean estimate of sensitivity and specificity in a ROC graph. Heterogeneity (between-study variation) of the results between studies was assessed graphically using Forest plots of sensitivity and specificity and was statistically quantified with the squared inconsistency index (I^2) test statistic, including 95% CI. The I^2 was calculated as follows: $I^2 = 100 \times [(Q - df) / Q]$, where Q is the Cochran heterogeneity statistic and df is the degree of freedom (44). The I^2 statistic expresses the percentage of total variation across studies caused by heterogeneity rather than chance. A higher percentage indicates greater heterogeneity (45–47). Publication bias was visually assessed for each CT sign using a scatterplot of the inverse of the square root of the effective sample size (ESS) vs. the diagnostic log odds ratios (lnDOR), which should have a symmetrical funnel shape when publication bias is absent. Publication bias was formally tested using a regression of lnDOR against $1/\text{ESS}^{1/2}$ and weighted according to the ESS, with $p < 0.10$ indicating significant asymmetry. Random effects model was applied to compare the risk for cancer in the presence of anti-TIF-1 γ autoantibody, compared with the presence of other MSA, in order to homogenize results. All statistical analyses were performed with R software (R, version 3.0.2, R Foundation for Statistical Computing) and RevMan software, version 5.3 (The Cochrane Collaboration, 2008, Copenhagen, Denmark).

¹<https://www.medicaljournals.se/acta/content/abstract/10.2340/00015555-3091>

RESULTS

Literature search and assessment of publication bias

In the initial search, 311 references were retrieved, 55 of which were duplicates. Hand-searching through the references in relevant articles did not turn up any additional material. Titles and abstracts of 256 papers were screened and 148 full-text references were selected. After a detailed review, and updating database between December 2017 and May 2018, 18 studies (13, 16–18, 20–22, 24–29, 31–35) were included in this meta-analysis (Fig. 1). Visual examination of the funnel plot revealed mild asymmetry, suggesting small publication bias (Fig. 2).

Meta-analysis

A total of 18 cohort studies with 1,962 DM met the inclusion criteria. The detailed characteristics are presented in Table S1¹. Included studies were cohort studies containing a median of 91 patients (range 20–376), all of whom were recruited after 1980. Fifteen studies selectively included adults (13, 17, 18, 20, 21, 24–29, 31, 32, 34, 35) and 3 studies (16, 22, 33) mainly included adult patients with a mean or median age in cohorts > 50 years. Mean follow-up (when reported) ranged from 1.8 (24) to 5.3 (28) years. A total of 363 cases of CAD were diagnosed in the total population.

Overall, anti-TIF-1 γ autoantibody was detected in 436 of 1,962 patients. In 5 studies (16–18, 24, 31), authors used IP with extracts of the K562 leukaemia cell line as the source of antigens and identified dual protein bands of 155 and 140 kDa, corresponding to the simultaneous presence of anti-TIF-1 γ and anti-TIF-1 α autoantibodies, respectively. Six other studies (20–22, 27–29) used extracts from a cervical cancer cell line (HeLa cells) exclusively and reported the IP of a single 155-kDa band corresponding to the presence of anti-TIF-1 γ autoantibody with or without anti-TIF-1 α antibody. Three studies (13, 25, 32) used IP with extracts of K562 or HeLa cells in assays and described the IP of a 155-kDa protein that was often, but not always, accompanied by a 140-kDa band. One of these studies used ELISA to confirm the IP results (32). One study used ELISA and IB assays to

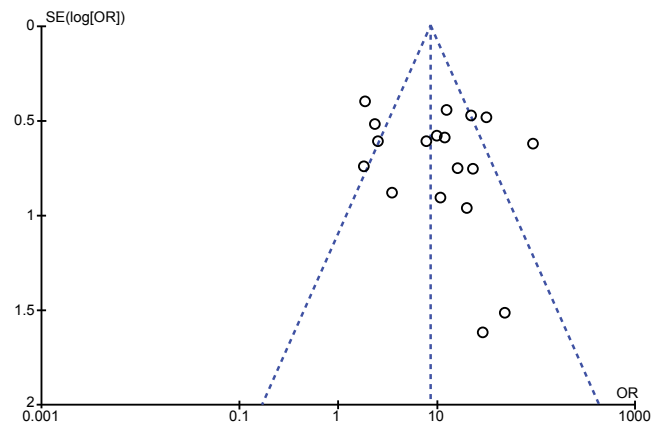


Fig. 2. Funnel plot for studies reporting the risk of cancer in the presence of anti-transcriptional intermediary factor-1 γ (anti-TIF-1 γ) autoantibody in adult dermatomyositis (DM). Funnel plot is used to assess publication bias. Points represent included studies. Visual examination shows slight asymmetry, suggesting small publication bias and low heterogeneity.

confirm the IP using HeLa cells results (26). One study (34) used only IB assay and one study (35) used only ELISA to detect the presence of anti-TIF-1 γ antibody, while one study (33) did not specify the method used to detect anti-TIF-1 γ autoantibody.

Eleven studies (17, 20–22, 25–29, 32, 33) specifically used the temporal criteria proposed by Troyanov et al. (48) to define CAD: cancer diagnosis within 3 years before or after DM diagnosis. Two studies (13, 24) applied the proposal of Love et al. (49) to define CAD as cancer diagnosed < 1 year after DM diagnosis. One study considered patients to have CAD for any malignancy 1 year preceding or 2 years after the beginning of DM symptoms (34). One study retained the diagnosis of CAD if the cancer was diagnosed “shortly” after DM (18). In 3 studies (16, 31, 35), the definition of CAD was not reported, but the authors provided sufficient information regarding the diagnosis schedule.

Methodological quality

The quality of the studies according to the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) (41) tool is reported in Table SII¹ and Fig. S1¹. The quality

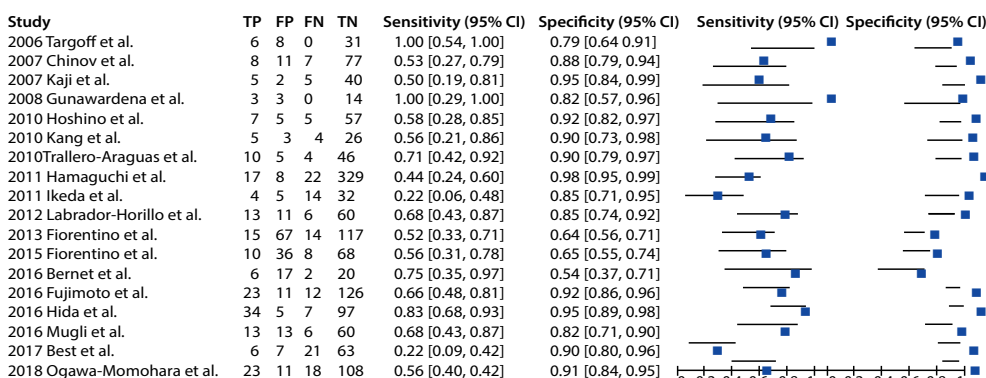


Fig. 3. Forest plots of estimated sensitivity and specificity of anti-transcriptional intermediary factor-1 γ (anti-TIF-1 γ) autoantibody testing for diagnosis of cancer-associated dermatomyositis. FN: false negative; FP: false positive; TN: true negative; TP: true positive. Squares represent the point estimates from each study; horizontal lines show the 95% confidence intervals (95% CI).

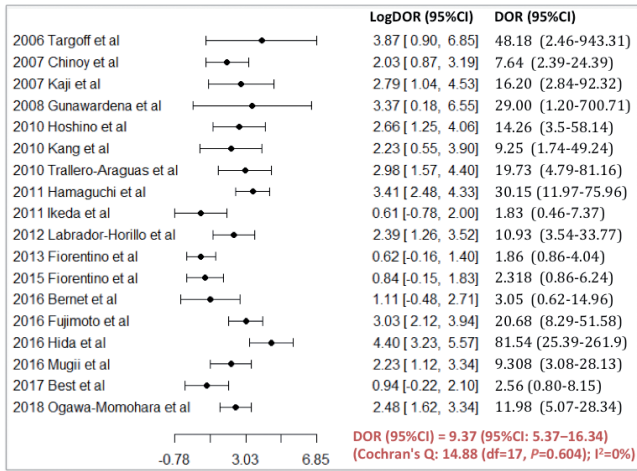


Fig. 4. Forest plots of estimated log diagnostic odds ratios (DOR) of cancer-associated dermatomyositis in the presence of anti-transcriptional intermediary factor-1γ (anti-TIF-1γ) autoantibody. Squares represent the point estimates from each study; horizontal lines show the 95% confidence intervals (CI).

of the included studies assessed by the QUADAS-2 tool was considered reasonable. Sources of potential risk of bias and applicability concerns were predominantly related to the reference standard, as almost half of the studies failed to report the detailed modalities of cancer screening.

Risk of cancer in patients with anti-TIF-1γ autoantibody

Among the 1,962 DM, 436 (22.2%) were positive for anti-TIF-1γ autoantibody. CAD was diagnosed in 18.5% (363/1,962) of patients. The pooled prevalence of CAD in patients with anti-TIF-1γ autoantibody was 0.407 (95% CI 0.36–0.45). Sensitivity values for the individual studies ranged from 0.22 to 1, and the pooled estimated

sensitivity was 0.52 (95% CI 0.47–0.57). Specificity values for the individual studies ranged from 0.54 to 0.98, and the pooled estimated specificity was 0.92 (95% CI 0.90–0.93) (Fig. 3). The global LR for a positive result of a test for TIF-1γ autoantibody was 4.2 across the studies. The global LR for a negative test result was 0.5. After pooling the data from the 18 published studies (13, 16–18, 20–22, 24–29, 31–35), we calculated an overall DOR for cancer in the presence of anti-TIF-1γ autoantibody of 9.37 (95% CI 5.37–16.34) with low heterogeneity (Cochran's Q: 14.88 (df=17, p=0.604); I²=0%) (Fig. 4).

Six studies (16, 17, 20, 21, 26, 35) including 107 patients with anti-TIF-1γ autoantibody out of 508 DM provided detailed data about the type of cancer. The prevalence of solid cancers and haematological malignancies in patients with DM across these studies was, respectively, 19.9% (101/508) and 1.4% (7/508). The pooled prevalence of solid cancers in patients with anti-TIF-1γ autoantibody was 0.56 (95% CI 0.46–0.66) corresponding to a DOR for solid cancers of 13.68 (95% CI 8.05–23.24) with low heterogeneity (Cochran's Q: 1.807 (df=5, p=0.875); I²=0%) and respective global LRs for positive and negative results of a test for TIF-1γ autoantibody of 5.34 and 0.44 across these studies. The pooled prevalence of haematological malignancies in patients with anti-TIF-1γ autoantibody was 0.01 (95% CI –0.06–0.08) corresponding to a DOR for haematological malignancies of 2.48 (95% CI 0.76–8.06) with low heterogeneity (Cochran's Q: 1.02 (df=5, p=0.961); I²=0%) and respective global LRs for positive and negative results of a test for TIF-1γ autoantibody of 1.86 and 0.77 across these studies.

In 6 studies (21, 22, 24, 25, 34, 35), the global OR for cancer in the presence of anti-TIF-1γ autoantibody, compared with the presence of anti-melanoma diffe-

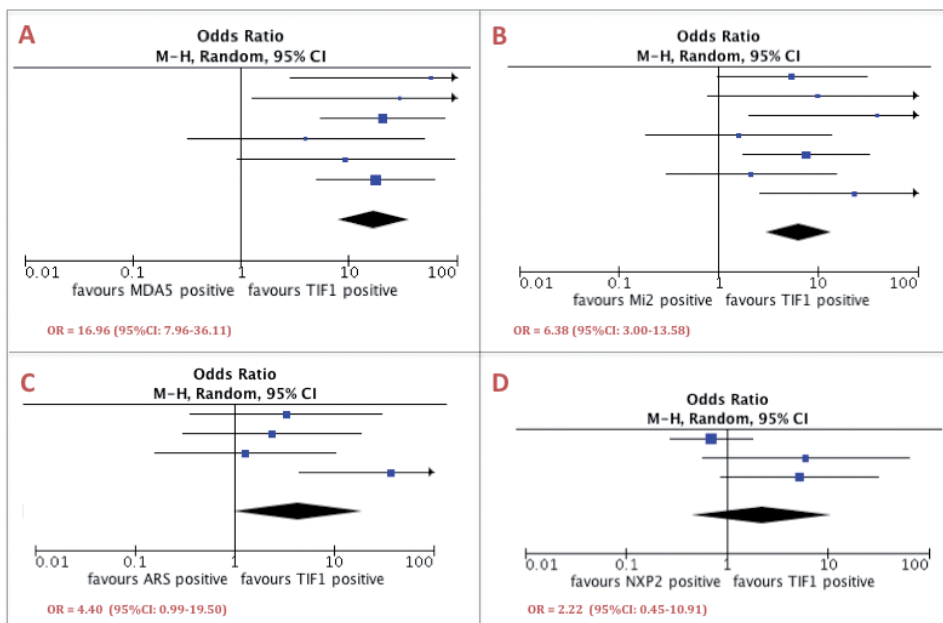


Fig. 5. Forest plots of estimated odds ratios of cancer-associated dermatomyositis in the presence of anti-transcriptional intermediary factor-1γ (anti-TIF-1γ) autoantibody compared with presence of: (A) anti-MDA5, (B) anti-Mi2, (C) anti-ARS, and (D) anti-NXP-2 autoantibodies. ARS: anti-aminoacyl-transfer RNA synthetase autoantibody; MDA5: anti-melanoma differentiation-associated protein 5 autoantibody; NXP2: anti-nuclear matrix protein-2 autoantibody; OR: odds ratio; TIF1: anti-transcriptional intermediary factor-1 gamma autoantibody. Squares represent the point estimates from each study; horizontal lines show the 95% confidence intervals (CI).

rentiation-associated protein 5 (MDA5) autoantibody, was 16.96 (95% CI 7.96–36.11) with low heterogeneity ($\chi^2=2.38$; $df=5$ ($p=0.79$); $I^2=0\%$) (Fig. 5A). In 7 studies (17, 21, 24, 25, 32, 34, 35), the global OR for cancer in the presence of anti-TIF-1 γ autoantibody, compared with presence of anti-Mi2 autoantibody, was 6.38 (95% CI 3.00–13.58) with low heterogeneity ($\chi^2=5.87$, $df=6$ ($p=0.44$); $I^2=0\%$) (Fig. 5B). In 4 studies (21, 25, 34, 35), the global OR for cancer in the presence of anti-TIF-1 γ autoantibody, compared with presence of anti-aminoacyl-transfer RNA synthetase (ARS) autoantibody, was 4.40 (95% CI 0.99–19.5) with high heterogeneity ($\chi^2=5.87$; $df=3$ ($p=0.12$); $I^2=49\%$) (Fig. 5C). In 3 studies (27, 34, 35) the global OR for cancer in the presence of anti-TIF-1 γ autoantibody compared with presence of anti-nuclear matrix protein-2 (NXP-2) autoantibody was 2.22 (95% CI 0.45–10.91) with high heterogeneity ($\chi^2=5.67$; $df=2$ ($p=0.06$); $I^2=65\%$) (Fig. 5D).

Among the 5 studies (16–18, 24, 31) that detected the simultaneous presence of anti-TIF-1 γ and anti-TIF-1 α autoantibodies by using the IP method with leukaemia cell line K562, an overall DOR for cancer in the presence of anti-TIF-1 γ/α autoantibodies of 14.91 (95% CI 8.18–27.18) was noted with low heterogeneity (Cochran's Q: 3.796 ($df=4$, $p=0.434$); $I^2=0\%$) and respective global LRs for positive and negative results of a test for anti-TIF-1 γ autoantibody of 6.32 and 0.48 across these studies (Fig. 6A). In 7 studies (20–22, 26–29) that detected only anti-TIF-1 γ autoantibody with or without anti-TIF-1 α autoantibody using HeLa cells for IP, the overall DOR for cancer in the presence of anti-TIF-1 γ autoantibody was 10.46 (95% CI 3.36–32.57) with high heterogeneity (Cochran's Q: 4.858 ($df=6$, $p=0.562$); $I^2=0\%$) and respective global LRs for positive and negative results of a test for anti-TIF-1 γ autoantibody of 4.63 and 0.41 across these studies (Fig. 6B).

DISCUSSION

This systematic review of the literature and meta-analysis pooling 18 studies (13, 16–18, 20–22, 24–29, 31–35) for

a total of 1,962 patients found that the presence of anti-TIF-1 γ autoantibody in adult patients with DM increases the risk of association with cancer with a DOR of 9.37 (95% CI 5.37–16.34). This result is consistent with the 2 previous meta-analyses showing, respectively, an OR for CAD of 27.26 (95% CI 6.59–118.82) (36) and an RR for CAD of 5.57 (95% CI 2.91–10.65) (12). The pooled sensitivity and specificity of anti-TIF-1 γ autoantibody for the diagnosis of CAD were 52% and 92%, respectively, suggesting that anti-TIF-1 γ autoantibody should be considered a valuable tool for predicting CAD in adult patients.

This study confirmed a higher prevalence of solid cancers (19.9%) than haematological malignancies (1.4%) in adult DM (4). Moreover, the absence of significantly increased risk of haematological malignancies in the presence of anti-TIF-1 γ autoantibody was noted, a result that needs to be confirmed in large prospective studies.

A higher risk of cancer in the presence of anti-TIF-1 γ autoantibody associated with anti-TIF-1 α autoantibody compared with anti-TIF-1 γ autoantibody alone was noted (i) by Fujimoto et al. (15) in a single cohort of 456 DM in which the frequencies of CAD in the presence of anti-TIF-1 γ/α autoantibodies and isolated anti-TIF-1 γ autoantibody were, respectively, 73% and 50% ($p<0.05$), and (ii) by Ogawa-Momohara et al. (35) in a cohort of 160 DM in which the frequencies of CAD in the presence of anti-TIF-1 γ/α autoantibodies and isolated anti-TIF-1 γ autoantibody were, respectively, 70% and 64% ($p=0.83$). Our meta-analysis seems to confirm this result with a DOR for CAD in the presence of anti-TIF-1 γ/α autoantibodies higher than the one calculated in the presence of the anti-TIF-1 γ autoantibody with or without anti-TIF-1 α autoantibody (14.9 vs 10.5). Because anti-TIF-1 γ autoantibody is currently detected by commercial immunodot kits without distinguishing the simultaneous presence of anti-TIF-1 α autoantibody, this analysis needs to be confirmed by large studies comparing the 2 IP methods.

Among the limitations of this meta-analysis are the differences between studies including: (i) variability in the criteria used to define adult DM; (ii) definition of

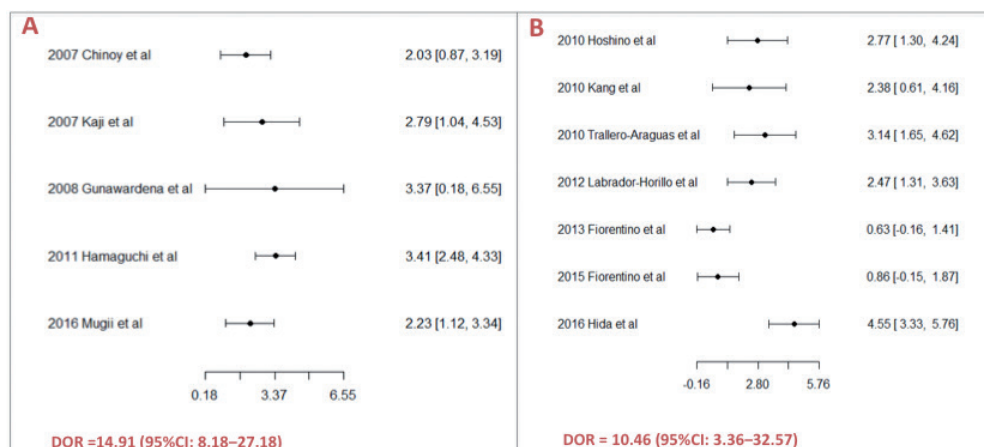


Fig. 6. Forest plots of estimated log diagnostic odds ratios (DORs) of cancer-associated dermatomyositis in the presence of anti-transcriptional intermediary factor-1 γ autoantibody among studies that used: (A) K562 cells; and (B) HeLa cells as the source of antigen in immunoprecipitation. Squares: point estimates from each study; horizontal lines: 95% confidence intervals (CI).

CAD; (iii) degree of completeness of cancer screening; (iv) immunological methods used to detect anti-TIF-1 autoantibodies; and (v) possible redundant data from some studies. The criteria of adult myopathic DM, defined by Bohan & Peter (37, 38), were systematically applied to the selected clinical cohorts. However, the “definite” criteria of DM for patient enrolment, including characteristic dermatological features of the DM rash and 3 other criteria, were specified in only 2 studies (21, 25), while the association of “definite” and “probable” (2 other criteria) DM criteria were applied in 9 studies (13, 17, 18, 20, 22, 26–28, 35), and no distinction between “definite”, “probable” or “possible” (1 other criterion) DM was noted in 7 studies (16, 24, 29, 31–34). Indeed, the sensitivity of Bohan & Peter’s criteria for the diagnosis of DM-polymyositis (PM) varies widely, based upon “definite” or “definite or probable” criteria (respectively, 66% and 89%) (50). One cohort study (21) explicitly excluded adult amyopathic DM (ADM) and 1 other study (13) did not specify whether ADM patients were included, causing a possible recruitment bias in our meta-analysis, although muscle involvement in DM does not appear to influence the risk of cancer in large series (12, 51). Likewise, the absence of restricted inclusion of adults (17, 22, 33) or a clear definition of the term “adult” (18, 20, 24–26, 31, 32, 35), or variability in the adult age definition, between >16 years (29) and >18 years (13, 17, 21, 27, 28, 34), may also have produced a recruitment bias in our meta-analysis. The frequency of CAD varied from 10.3% (24) to 32.7% (25). The definition of CAD is based on a temporal relationship between DM and cancer, which differed among the studies and could have caused heterogeneity in our analysis. The temporal criteria most often used are from Troyanov et al. (48), who defined patients with CAD as those whose cancer was diagnosed in the 3 years preceding or 3 years following the beginning of DM symptoms or DM diagnosis. These criteria were used in only 11 studies (17, 20–22, 25–29, 32, 33), suggesting that although all the cancer cases included fit within this timeframe, some may have been missed in other studies. Likewise, the modalities of cancer screening were not detailed in 10 studies (13, 17, 18, 20, 24, 26, 29, 32, 33, 35) and specific screening for gynaecological cancer was mentioned in only 3 studies (21, 22, 34). The prevalence of anti-TIF-1 γ autoantibodies in adult DM ranged from 6.6% (24) to 51.1% (33) a finding that highlights the high variability in immunological assays to detect MSA. Most of the studies used an IP method for anti-TIF-1 γ autoantibody detection, but IP remains an operator-dependent technique requiring a specialized centre, which may partly explain the differences in frequencies between studies. In order to increase the number of studies of our meta-analysis, we also considered line-blot and dot-blot assays because of their well-established performance to detect anti-TIF-1 γ autoantibody in comparison with the IP method (26, 52).

This systematic review found that detection of anti-TIF-1 γ autoantibody is a valuable tool to identify a subset of adult DM patients with a higher risk of cancer, thereby offering a more rational cancer screening approach in patients with DM. A simple generalized and standardized anti-TIF-1 γ assay will allow clinicians to establish more efficient protocols and algorithms to facilitate the detection of occult cancer in adult patients with DM.

The authors have no conflicts of interest to declare.

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