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REVIEW ARTICLE

Diagnostic and prognostic value of ARID1A in endometrial hyperplasia: a novel marker of occult cancer

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AT-rich interaction domain 1A (ARID1A) is a tumor suppressor protein involved in endometrioid carcinogenesis. The expression of ARID1A may be lost in the premalignant phase. Our aim was to assess ARID1A as: (i) diagnostic marker to differentiate premalignant endometrial hyperplasia (EH) form benign EH; (ii) prognostic marker for the risk of occult cancer in premalignant EH. A systematic review and meta-analysis were performed by searching electronic databases from their inception to October 2018 for all studies assessing ARID1A in EH by immunohistochemistry. Sensitivity, specificity, positive and negative likelihood ratios (LR+ and LR−), and diagnostic odds ratio (DOR) were calculated for both diagnostic and prognostic accuracy. LR+ > 5, LR− < 0.2, DOR > 25 defined good accuracy; LR+ > 10, LR− < 0.1, DOR > 100 defined excellent accuracy. Seven studies with 467 EH were included. As diagnostic marker, ARID1A showed sensitivity = 0.12, specificity = 0.99, LR+ = 4.34, LR− = 0.85, DOR = 5.12. As prognostic marker for occult cancer, ARID1A showed sensitivity = 0.33, specificity = 0.99, LR+ = 20.70, LR− = 0.49, DOR = 49.59. In conclusion, ARID1A loss is highly specific, but little accurate as diagnostic marker of premalignant EH. Instead, ARID1A loss in premalignant EH is an accurate and almost perfectly specific prognostic marker for coexistent cancer.

Key words: AT-rich interaction domain 1A; endometrial hyperplasia; endometrial intraepithelial neoplasia; cancer risk.

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Endometrial hyperplasia (EH) is a pathology characterized by hyperplastic changes in endometrial glandular and stromal structures lining the uterine cavity (1), (2). EH may represent either a functional proliferation (caused by unopposed estrogens action) or a premalignant lesion (driven by genetic mutations) (1–3). Premalignant EH can progress to endometrial carcinoma (EC) of endometrioid type (3), (3).

The distinction between benign and premalignant EH is crucial in terms of the choice of treatment. Benign EH may be managed by follow-up alone or by progestogens when symptomatic. Premalignant EH requires total hysterectomy; a conservative approach based on progestogens may be chosen in selected cases (4). The differential diagnosis is performed by histologic examination. Two alternative classification systems have been proposed for this purpose (2), (3). The WHO system differentiates 'atypical EH' (premalignant) from 'non-atypical EH' (benign), based on the presence of cytologic atypia (1), (2), (5), (6). The endometrial intraepithelial neoplasia (EIN) system differentiate 'EIN' (premalignant) from 'benign EH' based on glandular crowing, lesion diameter > 1 mm and cytology different from adjacent endometrium, careful exclusion of benign mimics and cancer (2), (3), (5), (6).

However, histologic diagnosis of EH is known to be difficult and affected by several issues, such as inter-observer variability, unclear features, or tissue paucity particularly in biopsy specimens (2), (7). To overcome misdiagnosis, molecular biology and the

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less expensive immunohistochemistry have been more and more at the heart of researches (8). In fact, many different studies have been conducted and a great number of biomarkers have been investigated to help pathologists in differentiating premalignant from benign lesions (2). One of the most interesting immunohistochemical marker has been AT-rich interaction domain 1A (ARID1A), a tumor suppressor protein which can be deficient in EC, particularly in the endometrioid type (2). Despite being proposed by 2017 ESGO guidelines as a useful marker in EH (9), its relevance as a diagnostic or prognostic marker has never been defined.

The aim of our study was to define the clinical usefulness of ARID1A in two different fields: (i) as a diagnostic marker to differentiate premalignant EH from benign EH, by calculating its diagnostic accuracy; (ii) as a prognostic marker for the risk of cancer in EH, by calculating its prognostic accuracy.

MATERIALS AND METHODS

Study design

Methods for electronic search, study selection, risk of bias assessment, data extraction and data analysis were defined *a priori*. All review stages were conducted independently by three authors (AR, AT, MC). Any disagreement was resolved by discussion with a fourth author (GS).

The study was reported according to the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement (10).

Search strategy and study selection

MEDLINE, Scopus, Web of Sciences, and Google Scholar were searched for relevant articles from the inception of each database to October 2018. Several different combinations of the following text words were used: 'endometrial hyperplasia'; 'endometrial intraepithelial neoplasia'; 'endometrial cancer'; 'EIN'; 'precancer'; 'premalignant'; 'precursor'; 'ARID1A'; 'AT-rich interaction domain 1A'; 'BAF250'; 'marker'; 'biomarker'; 'immunohistochemistry'; 'immunohistochemical'. References of relevant articles were also reviewed.

All peer-reviewed, retrospective or prospective studies, assessing immunohistochemical expression of ARID1A on histological specimen of EH were included in the systematic review. Exclusion criteria were as follows: case reports, reviews, overlapping patient data with a study already included.

Risk of bias assessment

The risk of bias assessment was based on the revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) (11). Four domains were assessed in each study: (i) patient selection (i.e., if the patients were consecutive); (ii) index test (i.e., if the assessment of ARID1A expression were unbiased), (iii) reference standard (i.e., if the histomorphologic classification was unbiased), (iv) flow and timing (i.e., if all patients were assessed with the same tests; if all patients were assessed with both index and reference tests). Authors' judgments were categorized as: 'low risk' (adequate methods), 'high risk' (inadequate methods), or 'unclear risk of bias' (unclear adequacy of methods, information not reported).

Data extraction

Data from each eligible study were not modified during the extraction. For both diagnostic and prognostic accuracy assessment, two by two contingency tables were elaborated, considering two qualitative variables:

1. immunohistochemical expression of ARID1A, dichotomized into 'presence' or 'loss' (for both diagnostic and prognostic accuracy assessment);
2. histologic category of EH, dichotomized into 'benign' or 'premalignant' (for only diagnostic accuracy assessment);
3. presence of cancer coexistent with EH, dichotomized into 'cancer' or 'no cancer' (for only prognostic accuracy assessment).

ARID1A 'loss' was defined as a wide and complete loss of immunostaining; the presence of only few ARID1A-null glands was considered as 'presence' instead.

'Benign' EH included non-atypical EH according to WHO and benign EH according to EIN system. As proposed in the literature (12), the WHO category of 'disordered proliferative endometrium' was considered as 'benign' EH, because it constitutes a pathologic continuum with non-atypical EH and it is classified as benign EH by the EIN system (1), (5). 'Premalignant' EH included atypical EH according to WHO system and EIN according to EIN system.

Regarding the presence of EC coexistent with premalignant EH, 'cancer' indicated the presence of an occult EC missed on initial biopsy and subsequently found on histologic examination of hysterectomy specimen.

For meta-analysis of diagnostic accuracy, the index test was the immunohistochemical expression of ARID1A ('presence' or 'loss'), while the reference test was the histologic category of EH ('benign' or 'premalignant').

For the meta-analysis of prognostic accuracy, the index test was the same as diagnostic accuracy evaluation, while the reference standard was the presence of cancer coexistent with EH ('cancer' or 'no cancer'). In the diagnostic accuracy analysis, premalignant EHs with ARID1A loss were considered as 'true positive', benign EHs with ARID1A loss as 'false positive', benign EHs with ARID1A presence as 'true negative', and premalignant EHs with ARID1A present as 'false negative'.

In the prognostic accuracy analysis, EHs with ARID1A loss and cancer were considered as 'true positive', EHs with ARID1A loss and no cancer as 'false positive', EHs with ARID1A presence and no cancer as 'true negative', and EHs with ARID1A presence and cancer as 'false negative'.

Data analysis

For both diagnostic and prognostic accuracy, sensitivity, specificity, positive and negative likelihood ratios (LR+ and LR−), and diagnostic odds ratio (DOR) were calculated with 95% confidence intervals (CI). As suggested in the literature, LR+ > 5, LR− < 0.2, and DOR > 25 were used to define good accuracy, while LR+ > 10, LR− < 0.1, and DOR > 100 were used to define excellent accuracy (13), (14).

For the diagnostic accuracy evaluation, all studies assessing premalignant EHs were suitable for the sensitivity analysis; all studies assessing benign EHs were suitable for the specificity analysis; only the studies assessing both benign and premalignant EH were suitable for analysis of LR+, LR−, and DOR.

Statistical heterogeneity among studies was quantified by using the inconsistency index (I^2): heterogeneity was considered insignificant for $I^2 < 25\%$, low for $I^2 < 50\%$, moderate for $I^2 < 75\%$, and high for $I^2 \geq 75\%$. The random effect model of DerSimonian and Laird was used, because heterogeneity is expected in meta-analysis of diagnostic accuracy (14). Results were reported graphically on forest plots.

The data analysis was performed using Review Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, Cochrane Collaboration, 2014) and Meta-DiSc version 1.4 (Clinical Biostatistics Unit, Ramon y Cajal Hospital, Madrid, Spain).

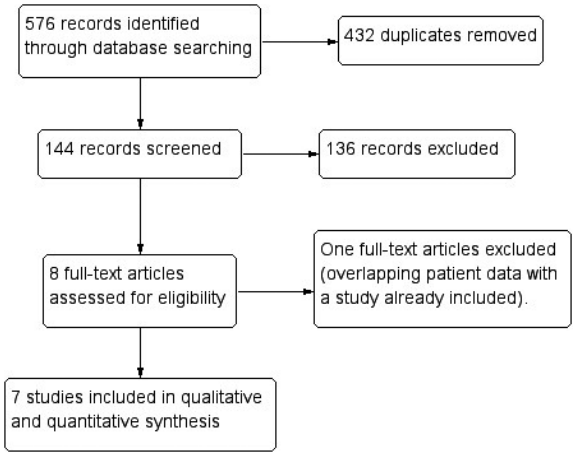

Fig. 1. Flow diagram of studies identified in the systematic review (Prisma template [Preferred Reporting Item for Systematic Reviews and Meta-analyses]).

RESULTS

Selection and characteristics of the studies

At the end of the study selection process, seven studies were finally included in the systematic review (15–21) (Fig. 1). One study (22) was excluded because it assessed the same sample as another included study (19). The total sample size was 1429, including 467 EHs. Sixty-seven EHs were benign and 400 were premalignant. Six studies collected the specimen retrospectively and one prospectively. Sampling methods included hysteroscopic biopsy, dilation and curettage, and hysterectomy. Six studies adopted the WHO classification system and one study the EIN system.

Table 1. Characteristics of the included studies

Study	Country	Study design	Period of enrollment	Sample size	Age	Diagnosis					Sampling method	Antibody
						NE	EP	B-EH	P-EH	EC		
Werner et al. (2013) (12)	Norway	Prospective	2001–2009	573	n.r.	0	0	7	31	535	Hysterectomy	Biosite, AT1188a
Mao et al. (2013) (13)	Taiwan, USA	Retrospective	n.r.	256	33–83	51	14	10	38	143	Curettage, hysterectomy	Sigma-Aldrich HPA005456
Zheng et al. (2014) (14)	China	Retrospective	2008–2010	134	>18	20	0	20	20	74	Hysterectomy, biopsy	Santa Cruz Bio-technology sc-32761
Ayhan et al. (2015) (15)	Japan, Taiwan	Retrospective	n.r.	114	20–78	0	0	0	114	0	Biopsy, curettage	Sigma-Aldrich HPA005456
Vierkoetter et al. (2018) (16)	USA	Retrospective	2009–2014	95	n.r.	0	0	0	95	0	Biopsy, curettage, hysterectomy	Abcam, Cambridge EPR13501MA
Niskakoski et al. (2018) (17)	Finland	Retrospective	1996-?	160	n.r.	22	0	30	50	58	Biopsy, hysterectomy	Sigma-Aldrich HPA005456
Yen et al. (2018) (18)	USA	Retrospective	2005–2017	97	58.9 (loss) 57.2 (retain)	0	0	0	52	45	Biopsy, curettage, hysterectomy	Sigma-Aldrich HPA005456
Total	–	–	–	1429	-	93	14	67	400	855	–	–

n.r., not reported; –, not appropriate; NE, normal endometrium; EP, endometrial polyp; B-EH, benign endometrial hyperplasia; P-EH, premalignant endometrial hyperplasia; EC, endometrial cancer.

Characteristics of the included studies are detailed in Table 1.

Risk of bias assessment

For the 'patient selection' domain, two studies were considered at low risk of bias, due to the inclusion of consecutive patients. The other studies were considered at unclear risk (information not reported).

For the 'index test' domain, unclear risk of bias was assigned to one study because criteria for immunohistochemistry interpretation were not clearly elucidated; the remaining studies were considered at low risk.

For the 'reference standard' domain, no particular risk of bias was pointed out, and all included studies were categorized at low risk.

For the 'flow and timing' domain, two studies were considered at unclear risk of bias (loss of patients unexplained (20) or unclear (15)) and 5 at low risk.

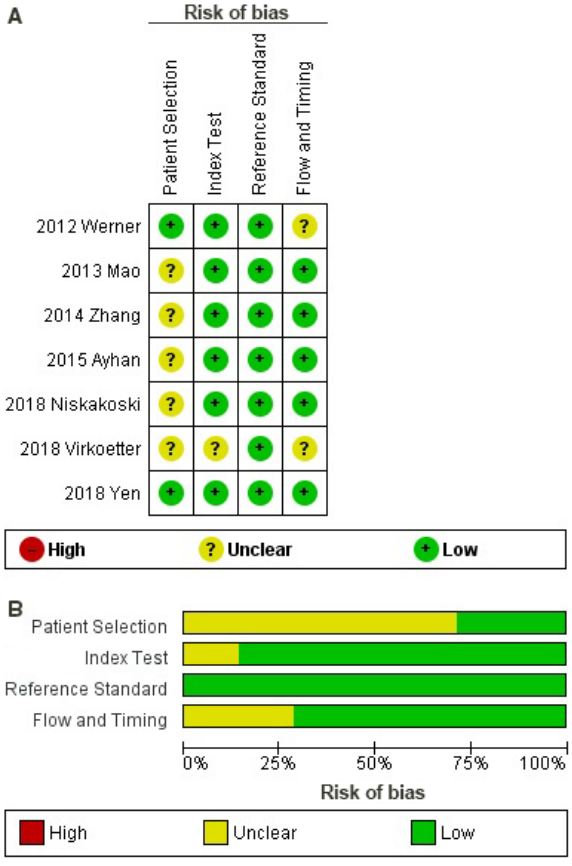

Fig. 2. (A) Assessment of risk of bias. Summary of risk of bias for each study; Plus sign: low risk of bias; minus sign: high risk of bias; question mark: unclear risk of bias. (B) Risk of bias graph about each risk of bias item presented as percentages across all included studies.

Authors' judgements are graphically reported in Fig. 2.

Diagnostic accuracy assessment

All studies were included in the analysis of sensitivity. As a marker of premalignant EH, ARID1A loss showed pooled sensitivity of 0.12 (95% CI, 0.09–0.15), with moderate heterogeneity among studies (I^2 = 60.6%).

Four studies were included in the analysis of specificity. Pooled specificity was 0.99 (95% CI, 0.92–1.00), with no heterogeneity among studies (I^2 = 0.0%).

Three studies were included in the analysis of LR+, LR−, and DOR. Pooled LR+ and LR− were 4.34 (95% CI, 1.06–17.74) and 0.85 (95% CI, 0.77–0.95), respectively, with no heterogeneity (I^2 = 0.0%) in both analyses. Pooled DOR was 5.12 (95% CI, 1.15–22.78), with no heterogeneity among studies (I^2 = 0.0%) (Fig. 3).

Prognostic accuracy assessment

Two studies were available for the analysis of the prognostic value of ARID1A in premalignant EH.

Pooled sensitivity and specificity of ARID1A loss for coexistent cancer were 0.33 (95% CI, 0.22–0.47) and 0.99 (95% CI, 0.94–1.00), respectively, with high (I^2 = 95.8%) and moderate (I^2 = 50.5%) heterogeneity, respectively.

Pooled LR+ and LR− were 20.70 (95% CI, 4.14–103.57) and 0.49 (95% CI, 0.07–3.27), respectively, with no (I^2 = 0.0%) and high heterogeneity (95.9%), respectively. Pooled DOR was 49.95 (8.46–294.8), with no heterogeneity (I^2 = 0.0%) (Fig. 4).

DISCUSSION

Main findings and interpretation

As a diagnostic marker of premalignant EH, ARID1A loss showed almost perfect specificity, but low sensitivity, resulting in a suboptimal accuracy. As a marker of coexistent cancer in premalignant EH, ARID1A showed good accuracy instead, with almost perfect specificity again.

ARID1A/BAF250 is a nuclear protein that participates in forming the SWI/SNF chromatin remodeling complex. The protein is involved in important cellular functions including transcription modulation, DNA damage repair, DNA synthesis, and DNA methylation. ARID1A acts as a tumor suppressor. Inactivating mutations of ARID1A result in loss of ARID1A protein expression, a common condition in EC (23).

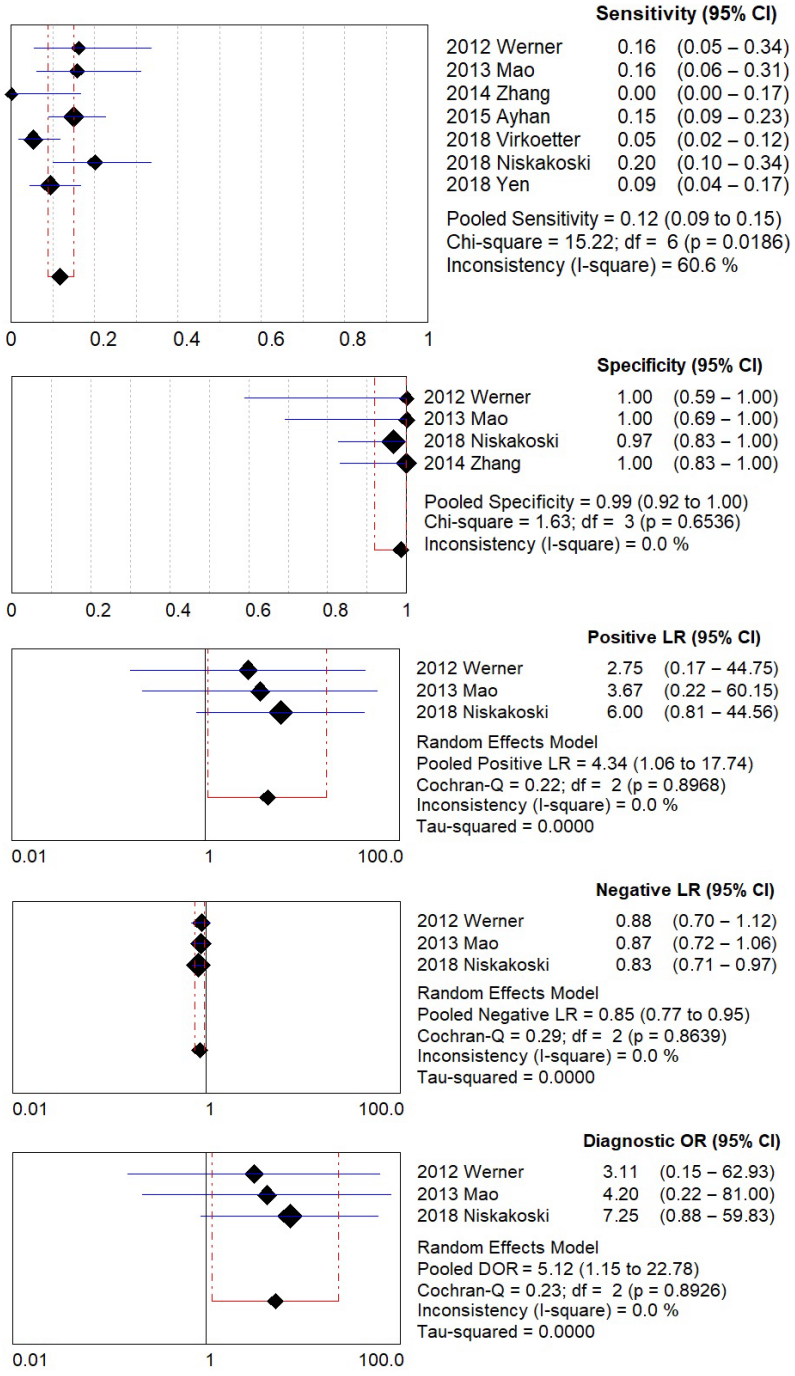

Fig. 3. Forest plots reporting sensitivity, specificity, positive and negative likelihood ratios, and diagnostic odds ratio of ARID1A as a diagnostic marker in the differential diagnosis between benign and premalignant endometrial hyperplasia.

ARID1A is one of the immunohistochemical marker proposed by the 2017 ESGO guidelines to differentiate premalignant EH from benign mimics (24). However, the diagnostic accuracy of immunohistochemistry for ARID1A is anything but defined. We found that ARID1A loss was very little sensitive (0.12) for premalignant EH. This finding resulted in a suboptimal diagnostic accuracy (LR+ = 4.34, LR− = 0.85, DOR = 5.12), making ARID1A inadequate as a diagnostic marker. On

the other hand, the specificity of ARID1A as a marker of premalignancy was almost perfect (0.99). For this reason, ARID1A does not appear adequate as a stand-alone diagnostic marker of premalignant EH, but it may be useful as a 'rule-in' test for diagnosis of precancer, due to its excellent specificity. In our previous studies, we found that Bcl-2 and PAX2 were specific marker of premalignant EH (25), (26). On the other hand, PTEN, which is considered the key molecule in endometrial carcinogenesis, was too little specific to be clinically useful (27–29). The combination of several specific markers might constitute a highly accurate test for EH diagnosis. An immunohistochemical panel of diagnostic markers might be a little expensive solution to improve the histologic diagnosis of EH, especially in difficult cases. Our results suggest not to use ARID1A as a stand-alone diagnostic marker. We think that information about the diagnostic accuracy of ARID1A should be provided in the next guidelines.

ARID1A has also been studied as a prognostic marker in EH. Some studies showed that the rates of ARID1A loss were higher in EC than in EH, indirectly supporting a prognostic relevance of ARID1A. Recently, the prognostic value of ARID1A has been assessed more specifically, by correlating its expression on preoperative EH

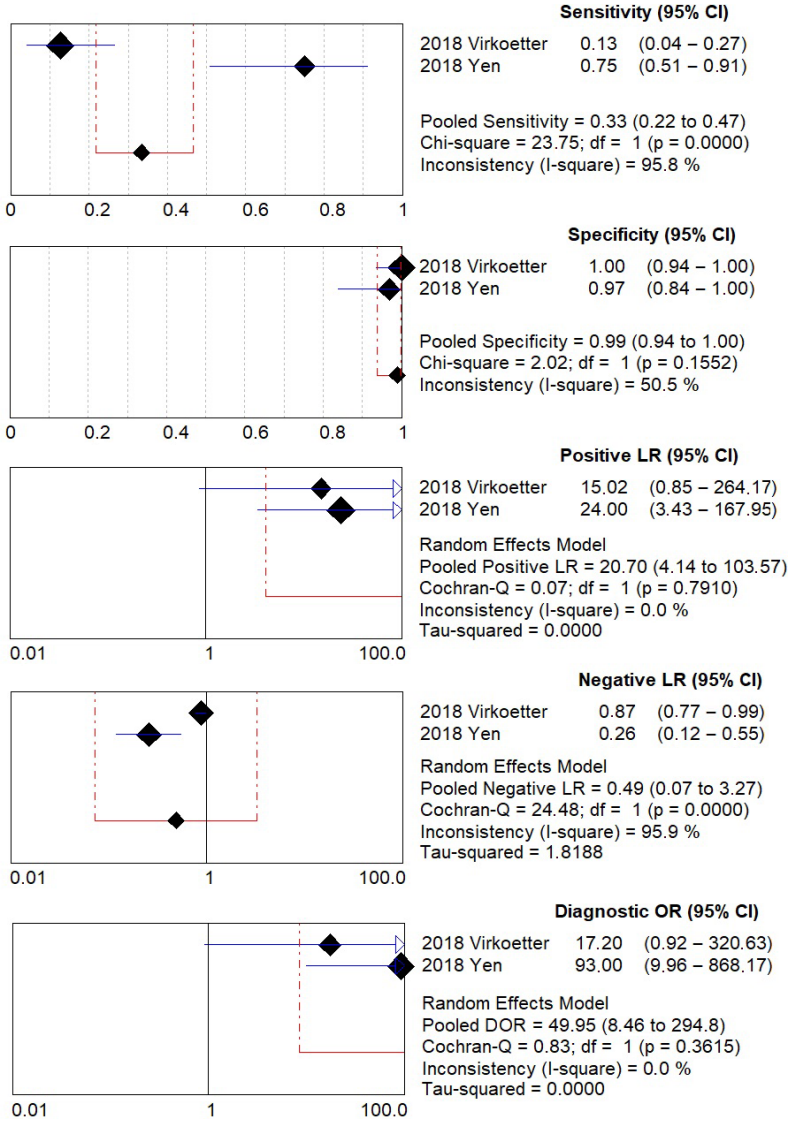

Fig. 4. Forest plots reporting sensitivity, specificity, positive and negative likelihood ratios, and diagnostic odds ratio of ARID1A as a prognostic marker for occult cancer coexisting with endometrial hyperplasia.

biopsies with the presence of occult cancer revealed on a subsequent hysterectomy. Our study focused on these novel data. We found that ARID1A loss in premalignant EH was highly specific (0.99) for coexistent cancer. Even in this case, sensitivity was found low (0.33), but the prognostic accuracy was good (DOR = 49.95). Furthermore, an excellent LR + was observed (20.70).

These results support the usefulness of ARID1A as a prognostic marker in EH. The excellent specificity and LR+ may make immunohistochemistry for ARID1A a valuable test to predict the presence of EC coexisting with premalignant EH. Based on the Fagan's nomogram, ARID1A loss in atypical EH/EIN may indicate a likelihood around 95% of occult cancer (Fig. 5). Immunohistochemistry for ARID1A may be crucial in the management of patients diagnosed with EH, identifying cases at very high risk of coexistent cancer. Firstly, ARID1A loss may indicate the need for a more careful diagnosis, in order not to miss an occult cancer. Secondly, in patients eligible for conservative treatment, ARID1A loss might lead to perform a more careful evaluation of eligibility and a closer follow-up, due to the high risk of cancer. In fact, ARID1A loss was found to be associated with myoinvasive EC (21). An intravenous contrast-enhanced abdomen and pelvis magnetic resonance (recommended for conservative treatment of EC, but not of EH) might be necessary in order to confirm the absence of myometrial or cervical invasion, as well as extrauterine metastases (30). Thirdly, ARID1A status may be crucial in the assessment of eligibility for conservative treatment in borderline cases, such as age around 40, pluriparity, wish to get pregnant not in the short term, low couple fertility potential. Finally, in patient eligible for hysterectomy, it might indicate a higher surgical priority. Given all these observations, ARID1A evaluation may add important diagnostic and prognostic information in order to adopt a more tailored approach to the patient. Such information may be even more important if we consider the wide range of available treatments for EH ad EC (31–34) and the inaccuracy of the predictive markers studied (35–39). To date, ARID1A appears as the most promising prognostic marker in EH. Indeed, although other immunohistochemical markers have been studied in this regard, including PTEN, Bcl2, PAX2, β-catenin, and COX2, none of them has shown a specificity comparable to ARID1A (40), (41); similarly, clinical markers associated with occult cancer in EH, such as diabetes mellitus, appear unsuitable to be used as stand alone for prognostic stratification (42). The loss of mismatch repair proteins expression might be another promising prognostic marker in EH, but its prevalence appears too low (43).Given its prognostic accuracy, ARID1A might be assessed independently from other markers and in all patents with premalignant EH.

Further studies are necessary to confirm the diagnostic and prognostic significance and the clinical applicability of immunohistochemistry for ARID1A in EH.

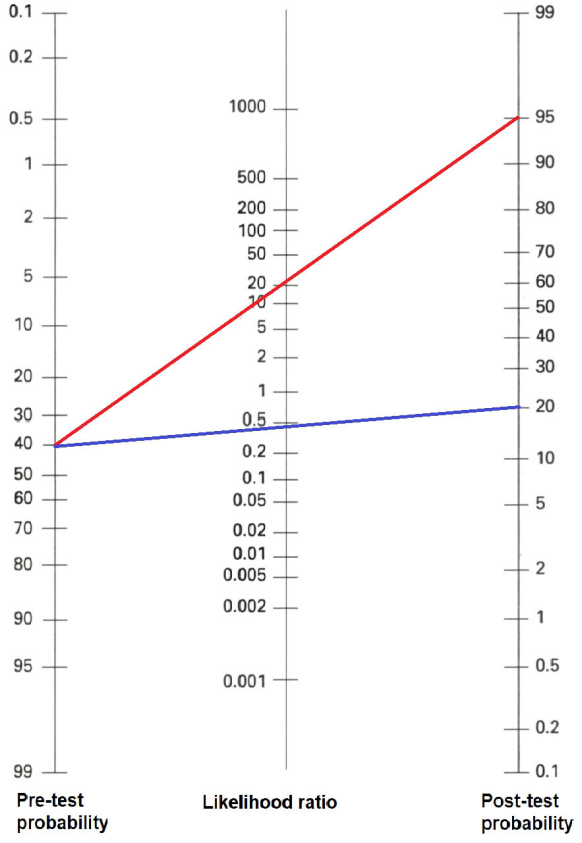

Fig. 5. Fagan's nomogram reporting pre-test and post-test probability of cancer coexisting with endometrial hyperplasia, in case of ARID1A loss (red line) and ARID1A retained (blue line) at immunohistochemistry.

Strengths and limitations

This is the first meta-analysis assessing the significance of ARID1A in EH. We assessed a large sample and highlighted the novel and promising findings regarding the prognostic value of ARID1A.

A limitation of our study may lie in the lack of a standardized method to interpret ARID1A immunohistochemistry. This may be the cause of the significant heterogeneity in the sensitivity analysis. We tried to reduce the heterogeneity by using

only data regarding a complete loss of ARID1A expression.

Another limitation is the presence of only two studies in analysis of the prognostic value of ARID1A; this affected the assessment of heterogeneity, leading to an inconsistence of >50% in the pooled specificity, despite the closeness of the values.

However, in both diagnostic and prognostic analysis, the results regarding specificity appeared to be robust, ranging from 0.97 to 1.00 in all studies.

CONCLUSION

As a diagnostic marker of premalignant EH, ARID1A loss has high specificity but low overall accuracy, with a possible usefulness as a support marker, particularly if integrated in an immunohistochemical diagnostic panel.

On the other hand, ARID1A loss in premalignant EH appears as an accurate and almost perfectly specific prognostic marker for coexistent cancer. Immunohistochemistry for ARID1A might be introduced in the clinical practice as a prognostic test in premalignant EH. ARID1A immunohistochemical status might be a crucial information for a more tailored management of patients, affecting conservative treatment, surgical priority of hysterectomy, and evaluation of eligibility for conservative approach in borderline cases.

Further studies are necessary to confirm the clinical applicability of ARID1A as a diagnostic and prognostic test in EH.

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DISCLOSURE OF INTEREST

The authors report no conflict of interest.

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