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REVIEW ARTICLE

Scoring systems for the evaluation of adnexal masses nature: current knowledge and clinical applications

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ABSTRACT

Adnexal masses are a common finding in women, with 20% of them developing at least one pelvic mass during their lifetime. There are more than 30 different subtypes of adnexal tumours, with multiple different subcategories, and the correct characterisation of the pelvic masses is of paramount importance to guide the correct management. On that basis, different algorithms and scoring systems have been developed to guide the clinical assessment. The first scoring system implemented into the clinical practice was the Risk of Malignancy Index, which combines ultrasound evaluation, menopausal status, and serum CA-125 levels. Today, current guidelines regarding female patients with adnexal masses include the application of International Ovarian Tumours Analysis simple rules, logistic regression model 1 (LR1) and LR2, OVERA, cancer ovarii non-invasive assessment of treating strategy, and assessment of Different Neoplasias in the adnexa. In this scenario, the choice of the scoring system for the discrimination between benign and malignant ovarian tumours can be complex when approaching patients with adnexal masses. This review aims to summarise the available evidence regarding the different scoring systems to provide a complete overview of the topic.

KEYWORDS

Adnexal mass; RMI; CPH-I; OVA1; IOTA; ovarian cancer

Introduction

Ovarian cancer is the most silent and deadly gynecological malignancies, because of the lack of clear symptoms and signs until its advanced stages (Jayson et al. 2014, Laganà, Sofo, et al. 2016) and the challenge to obtaining optimal cytoreduction in case of upfront debulking surgery (Vitale et al. 2013, Rossetti et al. 2016, Ghisoni et al. 2018). The Food and Drug Administration has recently recommended avoiding performing screening tests for ovarian cancer, due to serious concerns about sensitivity (SN), faulty reliability, and high numbers of inaccurate results (Curtin 1994, Glanc et al. 2017, Grossman et al. 2018, FDA Safety Communication 2019). Therefore, the early diagnosis and the appropriate management of this disease, including novel strategies of second-line chemotherapy (Dizon 2017, Barra et al. 2019), could successfully reduce mortality (Schorge et al. 2010, Terzic et al. 2014).

Similarly to what occurred for cervical cancer diagnosis (Vitale et al. 2016, Valenti et al. 2017), many serum tumours markers and scoring models have been developed and investigated from 1990 (Geomini et al. 2009, Giampaolino et al. 2019). On that basis, today there are many different algorithms and indexes introduced in the clinical practice to guide the evaluation of adnexal pathologies (Table 1). All the proposed tools are aimed to help in the distinction between benign and malignant ovarian masses, increasing the SN and specificity (SP) of the simple medical evaluation, particularly when the gynaecologist is not expert in ultrasound (American College of Obstetricians and Gynaecologists 2002, Bristow et al. 2002, Ueland et al. 2011, Terzic et al. 2013c). The availability of diagnostic algorithms and indexes for the evaluation of adnexal masses is of paramount importance, but, at the same time, the high number of possible tools may provide confusion in the operator and uncertain

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Table 1. Algorithms and study models in discrimination of adnexal masses.

Algorithm/study model name	Abbreviation	Year of introduction
Algorithms		
Risk of Malignancy Index	RMI	1990
Risk of Ovarian Cancer Algorithm	ROCA	1996
Risk of Ovarian Malignancy Algorithm	ROMA	2010
In Vitro Diagnostic Multivariate Index Assay (OVA1)	IVDMIA	2011
CoPenHagen Index	CPH-I	2015
OVA2	Overa®	2016
Cancer Ovarii Non Invasive assessment of Treating Strategy	CONATS index	2016
Triple screen		2017
Study Models		
IOTA Simple Rules	SRs	2008
IOTA Logistic Regression Model 1	IOTA LR1	2012
IOTA Logistic Regression Model 2	IOTA LR2	2012
IOTA Assessment of Different NEoplasias in the AdneXa	ADNEX	2014

regarding which tool has the best SN and SP, as well as, if there is a tool to prefer as compared the others. On that basis, we performed a review of the scoring systems for the evaluation of adnexal masses nature, intending to provide a summary of the available tools and show how a clear winner among them is not present. Conversely, the key element is to choose the best system that better fits with the available instruments and patients' data at the moment of the evaluation.

Table 2. Comparison between benign and malignant ovarian masses regarding the risk of malignancy indices (RMIs; Hayam et al. 2016).

	Cut-off value	AUC	Sensitivity	Specificity	PPV	NPV
RMI 1	>205	0.934	87.04%	83.33%	74.60%	92.00%
RMI 2	>189	0.915	83.33%	87.50%	78.90%	90.30%
RMI 3	>211	0.918	81.48%	87.50%	78.60%	89.40%
RMI 4	>315	0.907	79.63%	90.62%	82.70%	88.80%
RMI 5	>220	0.911	81.50%	92.70%	86.30%	89.90%
p Value			.648			

ROC: receiver operator characteristic curve; AUC: area under the curve; PPV: positive predictive value; NPV: negative predictive value.

Algorithms and indexes based on serum markers

Risk of malignancy index (RMI)

One of the first systems that were proposed for the pre-surgical classification of adnexal masses was the RMI, a specifically designed scoring system. Jacobs et al. (1990) proposed RMI-1 to help clinicians in the differential diagnosis of benign and malignant adnexal mass (Jacobs et al. 1990). It is a combination of ultrasound evaluation (U), menopausal status (M), and serum CA-125 level (RMI = U×M×CA-125). In 1996, the RMI-1 was slightly changed by Tingulstad et al. (Tingulstad et al. 1996) and finally named RMI-2, which in turn was modified again and subsequently introduced into the clinical practice in 1999 as RMI-3 (Tingulstad et al. 1999).

Different studies have shown that RMI can differentiate malignant from benign tumours, even with non-specific histopathologic characteristics (Terzic et al. 2013a, Ushijima et al. 2015), and many investigations were performed to identify the accuracy of each one of the listed RMIs (Terzic et al. 2014). Jacobs et al. (1990) reported an SN of 85% and an SP of 97% for an RMI cut-off level of 200 (Jacobs et al. 1990). This high SN and SP of RMI-2 and RMI-3 at the cut-off level of 200 were confirmed by Yamamoto et al. (Yamamoto et al. 2009). Respectively, the SN and SP were reported of 90.0% and 80.0% for RMI-2 and resulted in 82.6% and 86.4% for RMI-3. These results were comparable to those obtained by Tingulstad et al. (Tingulstad et al. 1999). The positive predictive values (PPV) of RMI-2 and RMI-3 were 49.3% and 52.5%, respectively (Yamamoto et al. 2009), lower than those reported in previous studies (Andersen et al. 2003, Obeidat et al. 2004). Based on these results, Yamamoto et al. (Yamamoto et al. 2009) proposed the RMI-4 by including an additional ultrasound parameter in the RMI-1 formula: the tumour size score (S). The RMI-4 at a cut-off level of 450 had an SP of 91.0%, an SN of 86.8%, a PPV of 63.5%, and a negative predictive value (NPV) of 97.5% (Yamamoto et al. 2009).

Nevertheless, the available pieces of evidence comparing the different RMIs reported no statistically significant differences between the 4 RMIs (Aktürk et al. 2011, Bouzari et al. 2011).

On that basis, to improve the SP, a new RMI-5 has been designed by adding Doppler blood flow of the ovarian mass to the calculation of the previous RMI (Karimi-Zarchi et al. 2015). However, no statistically significant differences were reported by the comparison of all the five RMIs (RMI 1–5; Table 2; Hayam et al. 2016). Consequently, RMI-1 was proposed as the standard for the preoperative differentiation between benign and malignant ovarian masses among the available RMIs (Hayam et al. 2016).

Noteworthy, some Authors tried to replace CA125 with HE4 but did not found improvement in the overall performance of RMI (Abdalla et al. 2017).

In summary, RMI reported a better prediction of malignancy as compared to other single parameters, such as history data, symptoms, imaging and biomarkers (Terzic et al. 2013b, 2013d, Javdekar and Maitra 2015), and some Authors recognised RMI as one of the best available tests for the diagnosis of malignant adnexal masses (Davies et al. 1993, Terzic et al. 2015). This was particularly supported for the triage of patients in a low resource setting, where complicated radiological and biochemical tools are not available, helping to facilitate the proper diagnosis and the referral to a centre with better expertise (Dora et al. 2017).

Risk of ovarian malignancy algorithm (ROMA)

The ROMA is a serum marker-based test for ovarian mass discrimination, which combines serum concentrations of the biomarkers CA 125 and HE4 with menopausal status. Moore

et al. (2010) were the first to recognise the diagnostic potential of the CA 125/HE4 test (Moore et al. 2010), that analysed in a logistic regression model helps to subdivide patients with a pelvic mass into high versus low-risk group for ovarian malignancy (Vitale, La Rosa, et al. 2017, Vitale et al. 2018).

It has been reported that ROMA has a higher SN for epithelial ovarian cancer compared to RMI (SN 94.3% vs. 84.6% at an SP of 75%; Moore et al. 2010), in particular in women affected by stage I and II ovarian cancers, where ROMA detected 85% and RMI 65% of the cases.

Different studies confirmed the complementary performance of HE4 and CA 125 and the increased diagnostic potential of the HE4/CA 125 combination of ROMA over the use of CA 125 alone (Abdel-Azeez et al. 2010). In the study of Holcomb et al. (Holcomb et al. 2011), the SN of CA 125 and HE4 for epithelial ovarian cancer discrimination was 83.3% and 88.9%, and the SP of CA 125 and HE4 was 59.5% and 91.8%, respectively. However, several groups reported conflicting results. A large prospective study of women diagnosed with a pelvic mass concluded that HE4 or ROMA did not improve the diagnostic accuracy as compared to the utilisation of CA 125 alone, suggesting that the performance of the CA 125/HE4 combination may be affected by the variations in the target population (Van Gorp et al. 2011). Therefore, the comparative performance of ROMA versus RMI remains a point of concern, as well as the HE4/CA 125 combination versus CA 125 alone (Terzic et al. 2015).

Copenhagen index (CPH-I)

The CPH-I is based on the evaluation of serum CA125 level, serum HE4 level and the patient's age (Karlsen et al. 2015). CPH-I can be easily performed in primary and secondary health services in case of suspicious ovarian masses on ultrasound or another imaging scan and, therefore, contribute to refer patients to a specialised cancer centre.

Karlsen et al. showed that CPH-I was highly capable to discriminate benign from malignant ovarian disease (Karlsen et al. 2015). The SN and SP of CPH-I were 95.0% and 78.4% in the training cohort, and 82.0% and 88.4% in the validation cohort, respectively. Høgdall et al. have shown that ROMA, RMI, and CPH-I are all valid for the differentiation between women with benign and malignant ovarian tumours (Høgdall 2016). Furthermore, a Brazilian study independently applied ROMA and CPH-I in a population of 384 patients, 87 of which affected by ovarian cancer: the authors concluded that CPH-I and ROMA performed equally well for the discrimination of ovarian cancer from benign ovarian tumours (Yoshida et al. 2016). However, some Authors claimed caution since the SN of CPH-I may be as low as 70% and incorrect interpretation of results can, in turn, lead to a delayed referral of a woman to a specialised cancer centre (Terzic et al. 2013d).

Triple screen

A Triple screen is a newly designed algorithm, which relies on symptoms and abnormal serum tumour markers in postmenopausal women. The test measures three specific variables: patient symptoms, serum CA 125 and HE4 levels. The authors developed a very simple algorithm, including a self-administered symptom index (SI) with serum CA 125 and HE4 to define ovarian cancer risk (Goff et al. 2017). SI is considered positive if a woman reports 12 or more times per month, from less than one year, at least one symptom among bloating, increased abdominal size, difficulty eating, a quick feeling of full, and pelvic or abdominal pain. This triple screen was reported having an SN similar to the risk of ovarian malignancy index of CA 125 alone but with higher SP and PPV (Schorge et al. 2010, Lennox et al. 2015s). A triple screen is defined positive if at least two out of the three markers are abnormal (positive SI, CA $125 \geq 35$ U/mL, HE4 ≥ 140 pmol/L; Goff et al. 2017), and it is supposed that it can be offered without any special calculations or scoring systems by any practitioner.

Risk of ovarian cancer algorithm (ROCA)

The ROCA is a screening method based on the CA 125 serum level aimed to identify patients with an intermediate or elevated level of risk. ROCA was developed employing data from prospective screening trials in postmenopausal women including more than 22,000 women in the United Kingdom and more than 5000 women in Sweden. The analysis revealed a constant CA 125 serum level in the majority of women without ovarian cancer (Terzić et al. 2011); on the other hand, women affected by ovarian cancer showed a sharp increase in CA 125 values compared to the baseline level, that could not be explained by the background CA 125 fluctuations (Skates et al. 2001, Skates 2003). Elevated ROCA risk is defined by a significantly rising of CA 125 levels and is considered an indication to refer a woman to a transvaginal scan (TVS), meanwhile, it is considered normal in women with high but stable CA 125 levels (Skates 2012). Early-stage incident cases have been successfully identified by the ROCA with an SP of 99.9% (95% CI 599.7%, 100%) and PPV of 40% (95% CI 512.2%, 73.8%). Based on these results, some Authors suggested implementing strategies based on CA 125 for the early discrimination of ovarian cancer in postmenopausal patients (Lu et al. 2013). Recently, Naumann et al. (Naumann and Brown 2018) performed a study where demonstrated the usefulness of the ROCA test in improving the detection of early ovarian cancer. Nevertheless, as criticised by the FDA, the cost for the ROCA should be reduced tenfold to become useful in the general practice.

In vitro *diagnostic multivariate index assay (OVA1)*

The OVA1 test is an *in vitro* Diagnostic Multivariate Index Assay (IVDMIA) of Proteomic Biomarkers. In September 2009, OVA1 (Vermillion) has been the first *in vitro* diagnostic multivariate index test approved by the FDA (Zhang and Chan 2010) for the evaluation of ovarian cancer risk in women affected by ovarian masses. Nevertheless, the use of OVA1 is restricted to decide on the type of surgery that medical professionals need to apply (Zhang and Chan 2010).

The biomarkers included in the OVA1 (except CA 125) were detected through multicenter proteomic studies (Zhang and Chan 2010). The test has an overall SN of 92.2% as a stand-alone test and rises to 98.1% when performed in association with ultrasound imaging and physical examination (Longoria et al. 2014). The SN of OVA1 is considerably higher for patients affected by early-stage ovarian cancer (Longoria et al. 2014), and the NPV ranges from 92.0% to 96.9 (Bristow et al. 2013, Goodrich et al. 2014). Nevertheless, the SN of OVA1 in premenopausal women is 88.2% when combined with ultrasound imaging and physical evaluation, whereas CA125 reaches only 47.1% (Longoria et al. 2014). Therefore, premenopausal women are at an increased risk of failure of early-stage disease diagnosis, resulting in increased mortality risk (National Cancer Institute n.d., Fung 2010, Bellia et al. 2016). A similar increase in mortality rate is shown in the case of recurrent disease (Laganà et al. 2015, Shibutani et al. 2017) or low-performance status, as an example is the elderly population (Schuurman et al. 2018, Vitale et al. 2019).

Due to the low SN in premenopausal women, the opinions regarding OVA1 are controversial, and further concerns about the usefulness of the OVA1 test emerged from a recent evaluation of the assay, that did not show improvement upon the performance of CA 125 alone in prediagnostic samples (Moore et al. 2019, Moore et al. 2012).

OVA2 (overa®)

In 2016, the FDA cleared Overa® as a second-generation index assay with the same indications of OVA1. It combines CA 125, HE4, apolipoprotein A1, follicle-stimulating hormone, and transferrin (Ueland 2017). Because the follicle-stimulating hormone is part of the panel, determining the menopausal status of patients is not required. The Overa® score ranges from 0.0 to 10.0 and has the following clinical interpretation: low risk of malignancy <5.0; high risk of malignancy ≥ 5.0. The Overa® reported an SN higher than 90% independently by the physician assessment even in premenopausal women. Moreover, a significant improvement was provided by the SP of OVA2 as compared to OVA1. SP of OVA2 was increased over the SP of OVA1 by 15%, moving from an SP of 54% to an SP of 69.1%. This increased by 13% of the women resulted as negative at the OVA2 compared to the OVA1 (Coleman et al. 2016).

Cancer ovarii non-invasive assessment of treating strategy (CONATS)

A newly designed index for the preoperative evaluation of patients with advanced epithelial ovarian cancer was developed in 2016 by a Danish study group. The multivariate model CONATS index takes into account HE4, age, and performance status, demonstrating an area under the curve (AUC) of 0.853 (Karlsen et al. 2016). According to the CONATS level, macro-radical primary debulking surgery should be achieved in the 60% of patients undergoing primary surgery (positive predictive value of 60%), resulting in a negative predictive value of 87.5%, SN of 68.3%, SP of 83.5%, and cut-off of 0.63 for the CONATS index (Karlsen et al. 2016). According to the authors' statement, the CONATS index is proposed as a tool easy to be employed at tertiary centres specialised in the treatment of epithelial ovarian cancer. Noteworthy, since CA125 was inferior to HE4 in the prediction of complete cytoreduction, it was excluded from the CONATS index due to an insignificant contribution to this model. It is supposed that the optimal treatment strategy of patients with advanced epithelial ovarian cancer could be improved by the evaluation of the CONATS index combined with radiological and/or laparoscopic findings (Karlsen et al. 2016). However, the CONATS index still requires to be validated in the clinical practice.

Algorithms and indexes based on ultrasound

International ovarian tumor analysis study models – simple rules, logistic regression model 1 (LR1), LR2

Concerning diagnostic imaging of adnexal masses, simple ultrasound-based rules including five items for predicting malignant tumours (M-rules) and five for predicting benign tumours (B-rules) have been presented by the International Ovarian Tumours Analysis (IOTA) group in 2008 (Table 1). If one or more M-rules with the absence of B-rules or B-rules with the absence of M-rules are present, the tumour is supposed to be malignant or benign, respectively. In a multicenter study, these rules have shown an SN of 95% and SP of 91% (Timmerman et al. 2008).

Interestingly, within the past eleven years, the pre-surgical classification of adnexal masses has been performed by the same group proposing logistic regression models and ultrasound-based predictive rules (Kaijser et al. 2014). IOTA studies demonstrated that these models offered much better performance in comparison with pre-existing risk models such as the RMI (Nunes et al. 2012, Van Holsbeke et al. 2012). IOTA group designed two relatively simple logistic regression models: LR1 and LR2 as the principal method for preoperative triage of women with adnexal masses (Nunes et al. 2012). Any qualified ultrasound examiner scanning women with adnexal masses should be able to retrieve information on the variables required for both models (Timmerman et al. 2008, Van Holsbeke et al. 2012, Nunes et al. 2012). The IOTA LR2 model was found to have SN higher than 90% and SP over 80%. Previous research has shown that the model LR2 had a diagnostic performance very similar to LR1, despite LR2 had only six variables compared to 12 variables of LR1. The lower number of variables needed for LR2 and its excellent performance makes it a more popular choice in clinical practice (Timmerman et al. 2008, Van Holsbeke et al. 2012, Nunes et al. 2012).

Nevertheless, the opinion of an expert ultrasound examiner is still considered to be the best method, or at least equivalent to LR1 and LR2, for diagnosing an ovarian mass (Meys et al. 2016). According to several studies, the IOTA algorithms have been reported to be better than both RMI and ROMA to distinguish between benign and malignant adnexal tumours (Kaijser et al. 2014, Meys et al. 2016, 2017).

Assessment of Different NEoplasias in the adneXa – ADNEX model

The ADNEX model takes three clinical and six radiologic features into consideration, to foresee the risks of benign ovarian tumours, borderline ovarian tumours, stage I ovarian cancer, stages II-IV ovarian cancer and ovarian metastasis. Therefore, the IOTA ADNEX model can help to differentiate benign from malignant tumours, as well as identify the histologic types and tumour spread (Van Calster et al. 2014).

ADNEX was reported able to distinguish stage I cancer from benign tumours and advanced-stage cancer very efficiently, although it did not distinguish borderline from secondary metastatic cancers with the same accuracy (Van Calster et al. 2014, Epstein et al. 2016).

Discussion

Ovarian masses are a common finding in women of all ages and require precise differentiation.

Although the diagnostic method of reference is the histological evaluation of the surgical specimen obtained after surgery for both benign (El Bishry et al. 2008, Laganà, Vitale, et al. 2016, Vitale, Sapia, et al. 2017) and malignant conditions (Cignini et al. 2017, Rossetti et al. 2017, Shiozaki et al. 2019), only an appropriate clinical/pre-operative discrimination between benign and malignant ovarian tumours allow a proper approach to patients affected by adnexal masses. The conservative management with observation alone is sufficient in the case of benign cysts, such as functional ovarian cysts, whereas suspected malignant cysts require an appropriate surgical approach (American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Gynecology 2016). This is of paramount importance in benign pathologies related to enlarged ovaries, such as polycystic ovary syndrome, that has a different therapeutic approach (Chiofalo et al. 2017, Laganà et al. 2017, Reyes-Muñoz et al. 2018).

On that basis, the appropriate evaluation of adnexal masses is of paramount importance to define the subsequent clinical and/or surgical management. Therefore, to increase the accuracy of the adnexal mass evaluation and the discrimination between adnexal masses at risk of malignancy versus benign masses, within the past three decades different scoring systems/algorithms were developed based on tumour serum markers and imaging methods, incorporating multiple clinical, laboratory, and radiologic parameters.

As summarised in our review, no single diagnostic tool/approach has demonstrated higher reliability and higher validity for the clinical/preoperative prediction as compared to the others to allow a clear definition of the one of choice.

However, although the reported algorithms and indexes can be classified in those based on serum markers and in those based on ultrasound evaluation, it is clear that all require a diagnosis of adnexal mass and, therefore, the simple rules or LR2 are always feasible as first-line assessment and should be adopted in clinical practice as the principal test to characterise masses as benign or malignant according to the findings of the IOTA study (Timmerman et al. 2008). Moreover, of note, some Authors reported ultrasound parameters more informative and important than tumour markers (Van Gorp T et al. 2012).

However, if serum CA 125 and HE4 levels are available at the first evaluation, the Triple test and CHP-I could represent the first step to assess the risk before ultrasound characterisation. Conversely, the RMI, ROMA and ADNEX scores represent supportive tools to increase the diagnostic accuracy after the ultrasound assessment when serum tumours markers are available. Regarding the CA 125, it is of paramount importance to evaluate the absolute level as well as the trend as shown by the ROCA score. Finally, it should be highlighted the more limited role of OVA1, OVA2, and CONATS, that are primarily designed for the presurgical assessment and the choice of the surgical approach.

Although a clear recommendation on the most appropriate algorithm or index tool is not feasible, it is mandatory to remember the key role of further evaluation by experts gynaecologist as well as the use of further diagnostic tools, such as magnetic resonance, in case of suspicious adnexal mass with no clear or conflicting preliminary assessment.

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Disclosure statement

The authors have no conflicts of interest to declare.

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