Risk of Malignancy Index for Preoperative Evaluation of Pediatric Ovarian Tumors

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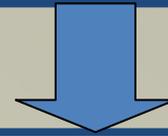
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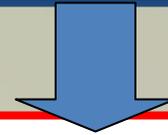KK Women's and Children's Hospital, Singapore

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Introduction
Background and aim

- **Aim: develop & validate risk-of-malignancy index for pediatric ovarian tumors**
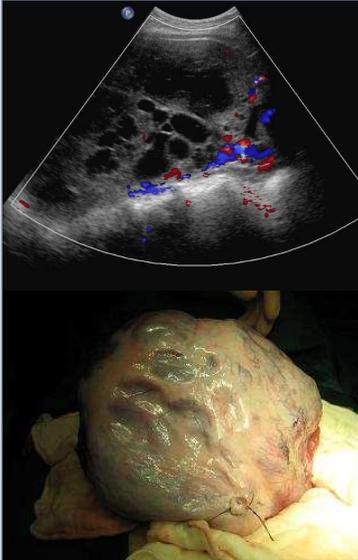
Existing prediction tools	Novel prediction tool
Adult Obgyn tumors	Childhood tumors
Screen detected	Acute presentation
Increasingly complicated	Based on accessible investigations

mathematical models

Materials & Methods
Scoring index development & validation

Development

Candidate variables

⬍

Histological outcome

Training set:
55 masses
(55 girls)

Validation

sensitivity, specificity,
NPV, PPV, LR+, LR-

Testing set:
15 masses
(14 girls)

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Materials & Methods
Scoring index development & validation

Development

Clinical, biochem, imaging features

Benign vs non-benign

Common features (CT, US)

Blinded score (consensus: 2 radiologists)

- Malignant
- Borderline
- Immature
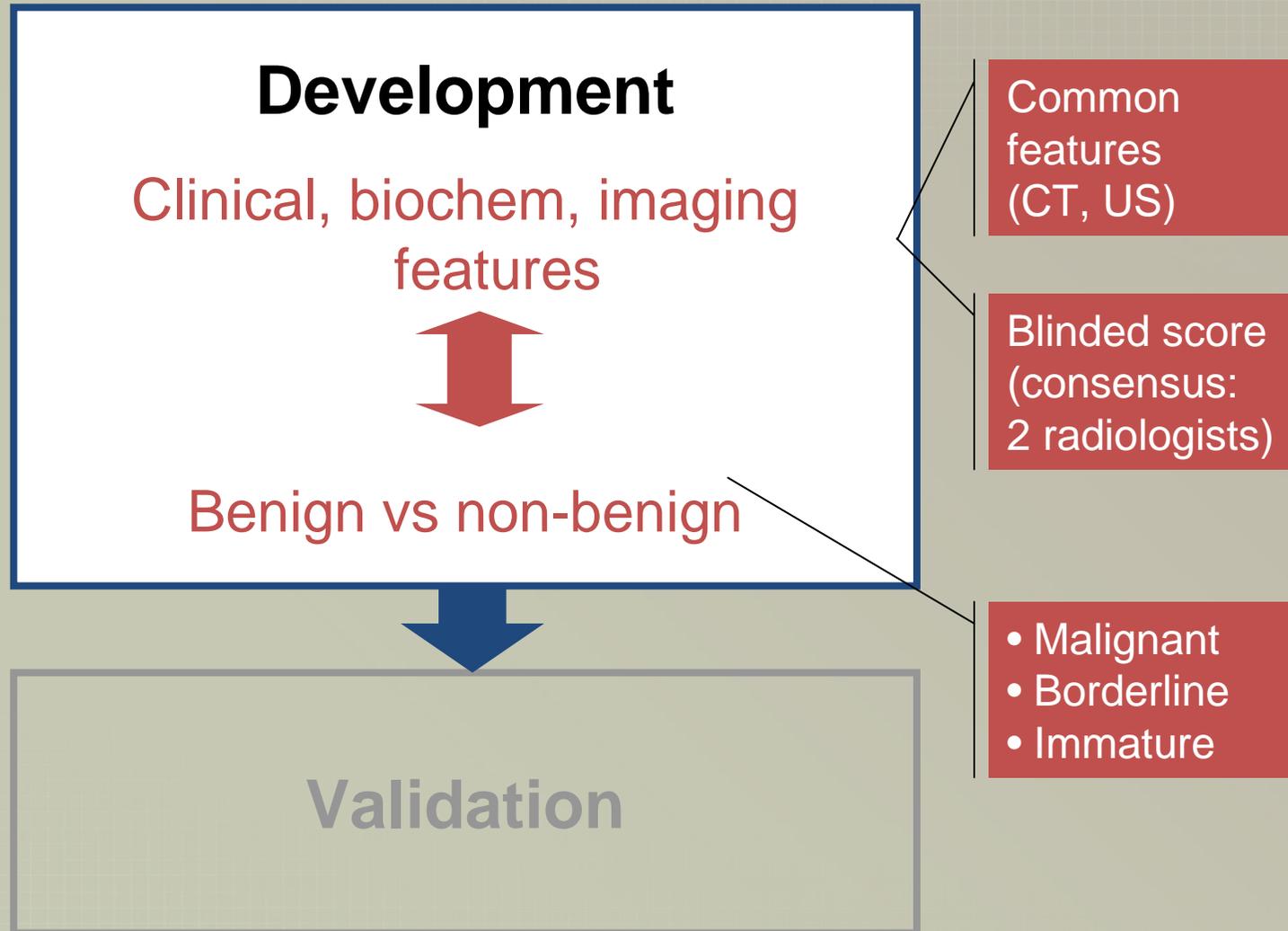
Validation

Materials & Methods
Scoring index development & validation

Development

Clinical, biochem, imaging features

Variable selection / reduction

Multivariate logistic regression

Benign vs non-benign

Predictive scoring indices

Areas under ROC curve

Select best score

Validation

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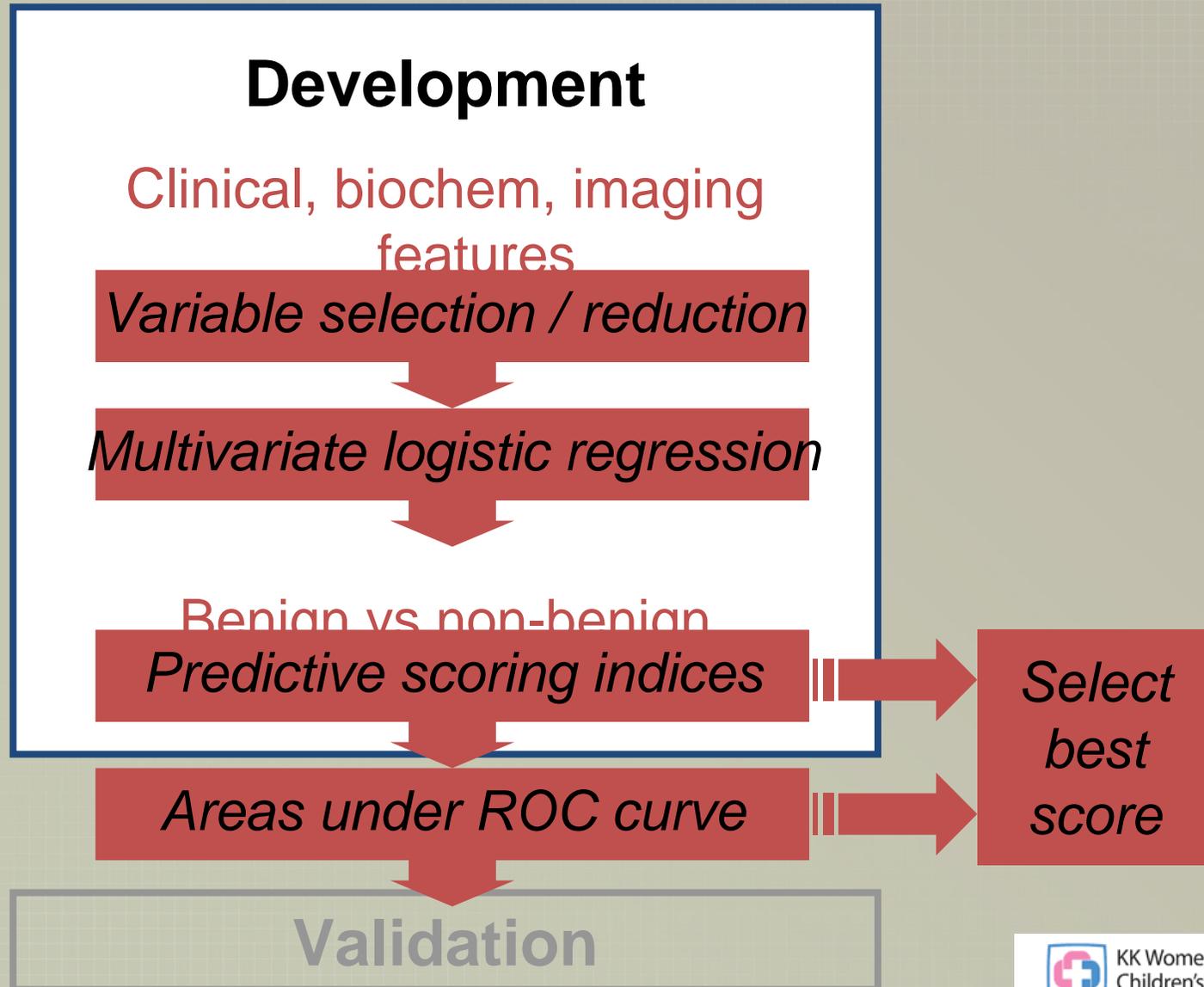
Materials & Methods

Study cohort: training set

Benign (n=47, 85%)		Non-benign (n=8, 15%)	
Serous cyst	2	Immature teratoma (with/without yolk sac component)	4
Mature teratoma	18		
Mixed seromucinous cystadenoma	1	Cystic mucinous tumor with borderline change	2
Serous cystadenoma	1		
Mucinous cystadenoma	1	Endodermal sinus tumor	1
Serous cystadenofibroma	1	Sex cord tumor with annular tubules	1
Follicular & luteal cysts (intact)	6		
Follicular & luteal cysts (hrr'gic)	8		
Cystic fibrous ovarian tissue	4		

Study cohort: testing set

Benign (n=13, 87%)		Non-benign (n=2, 13%)	
Serous cyst	1	Yolk sac tumor	1
Mature teratoma	1		
Serous cystadenoma	1	Sertoli-Leydig cell tumor	1
Follicular & luteal cysts (intact)	6		
Hemorrhagic / infarcted cysts	2		
Paratubal cyst	1		
Torted fallopian tube	1		

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Results

Variable		Values
Clinical		
Age		(years, less / greater than threshold)
Race		(Chinese / Malay / Indian / Others)
Menarche		(pre / post-menarche)
Presenting symptom	Pain	(absent / present)
	Painless mass	(absent / present)
	Hormonal symptoms	(absent / present)
	Incidental diagnosis on imaging	(absent / present)
Biochemistry	AFP	(ug/L, not raised / raised)
	BHCG	(IU/L, not raised / raised)
	CA125	(U/mL, not raised / raised)
	CEA	(U/mL, not raised / raised)
Imaging (CT or US)		
Max diameter of lesion		(cm, less / greater than threshold)
Max diameter of largest solid component		(cm, less / greater than threshold)
Loculation		(uniloculated / multiloculated or solid)
Septal structure		(<3mm / >3mm or solid lesion)
Enhancement or flow in septum or a solid papillary projection		(enhancement / no enhancement)
Ascites		(absent / present)
Irregular internal cyst wall		(absent / present)
Radiologist's subjective opinion		(benign / indeterminate or malignant)

Results

(training set)

Variable		Benign (%)	Non-benign	P
Clinical				
Presenting symptom	Painless mass	14.9	50.0	**.042**
	Hormonal symptoms	2.1	37.5	**.008**
Biochemistry	AFP (raised)	12.8	50.0	**.029**
	BHCG (raised)	2.1	12.5	.272
	CA125 (raised) *	13.2	83.3	**.001**
	CEA (raised) **	0.0	28.6	**.026**
Imaging (CT or US)				
Max diameter of lesion (cm) ***		8.20 ± 4.1	23.9 ± 11.9	**.007**
Max diameter of largest solid component (cm) ***		1.45 ± 2.4	6.0 ± 5.2	**.044**
Loculation (multiloculated or solid)		14.9	100.0	**<.001**
Septal structure (>3mm or solid)		21.3	87.5	**.001**
Enhancement or flow in septum or a solid papillary projection		23.4	37.5	.405
Ascites (present)		8.5	87.5	**<.001**
Irregular internal cyst wall (present)		4.3	50.0	**.018**
Radiologist's subjective opinion (indeterminate or malignant)		23.4	37.5	**.001**

*n=38 benign / 6 non-benign; **n=34 benign / 7 non-benign; ***Data presented as mean ± S.D

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Results

Variable	Coeff. (logO.R.)	S.E. of coeff.	Wald (chi-sq)	O.R. (95% C.I.)	P (2-tail)
Clinical					
Age 12 years and above	3.13	1.33	5.52	22.9 (1.7 - 313.1)	.019
Any elevated tumor marker *(AFP/BHCG/CEA/CA125)*	3.69	1.32	7.81	39.9 (3.0 - 530.2)	.005
Hormonal symptoms	5.08	1.91	7.12	161.0 (3.9 - 6730.9)	.008
Imaging					
NA (confounding from multicollinearity)			Score developed from ROC curves of significant univariate variables		

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Clinical score:

Variable	Criteria	Points
Age	12 and above	3
Tumor marker *(AFP/BHCG/CEA/CA125)*	Any raised	4
Hormonal symptoms	Present	5
	Total points	
	Non-benign outcome = Total points ≥ 9	

Imaging score *(un-weighted)*:

Variable	Criteria	Points
Maximum diameter of lesion, by age	> 70mm (up to 12 years old)	
	> 150mm (above 12years old)	1
Septal thickness	> 3mm or solid lesion	1
Loculation	Multiloculated or solid lesion	1
Internal irregular cyst wall	Present	1
Ascites	Present	1
Radiologist's impression	Indeterminate or malignant	1
	Total points	
	Non-benign outcome = Total points ≥ 4	

Results

Variable	Coeff. (logO.R.)	S.E. of coeff.	Wald (chi-sq)	O.R. (95% C.I.)	P (2-tail)
Clinico-radiological					
Max diameter of largest solid component	0.85	0.33	6.66	2.3 (1.2 - 4.4)	**.010**
Enhancement or flow in a septum or solid papillary projection	4.32	2.08	4.32	75.0 (1.3 - 4389)	**.038**
Hormonal symptoms	6.06	2.69	5.07	428.3 (2.2 - 83469)	**.024**

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Clinico-radiological score:

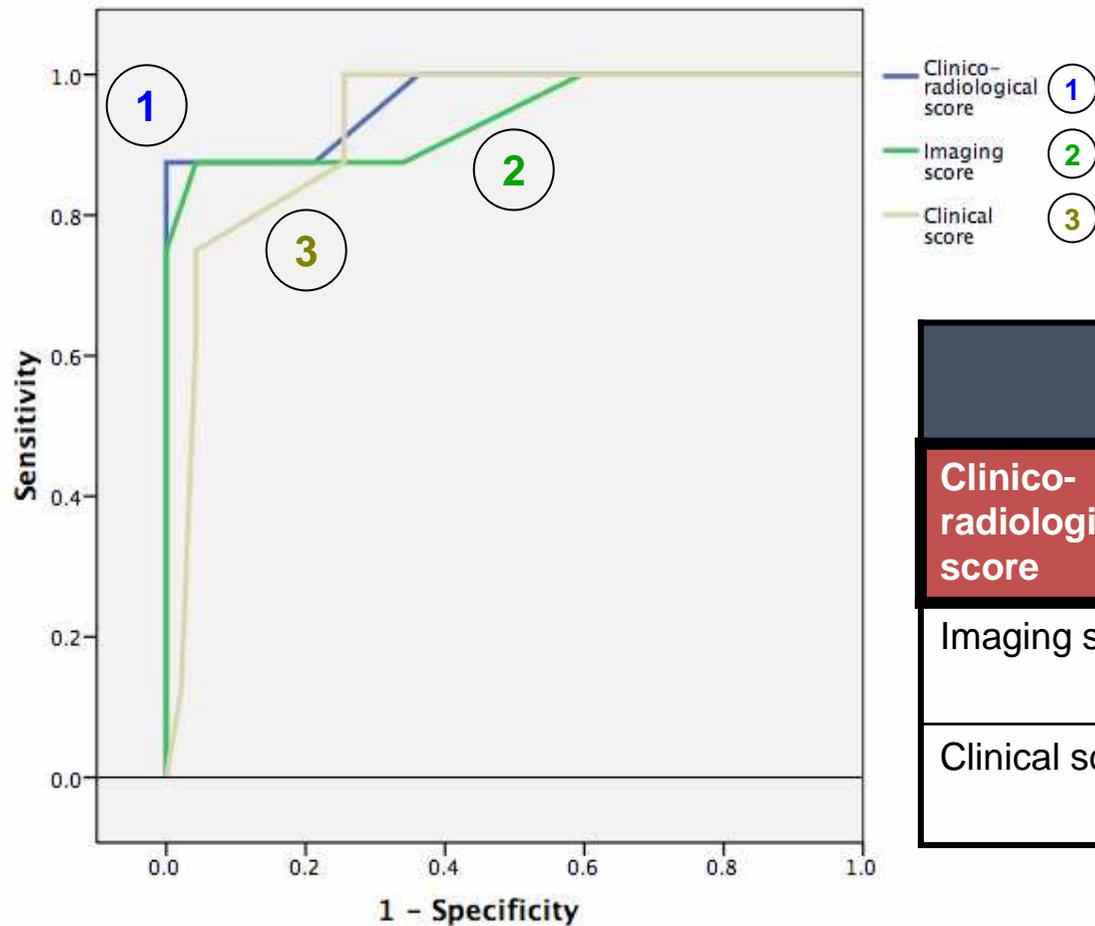| Variable	Criteria	Points
Max diameter of largest solid component	(cm)	(value in cm)
Enhancement / flow in a septum / solid papillary projection	Present	4
Hormonal symptoms	Present	6
	Total points	

Non-benign outcome = Total points ≥ 7

Results

curves

ROC curves of scoring indices

	Area under ROC curve	S.E.	95% C.I.
Clinico-radiological score	.964	.036	.894 - 1.034
Imaging score	.939	.057	.828 - 1.050
Clinical score	.927	.040	.849 - 1.005

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Modelled outcomes at cutoff value ≥ 7 points
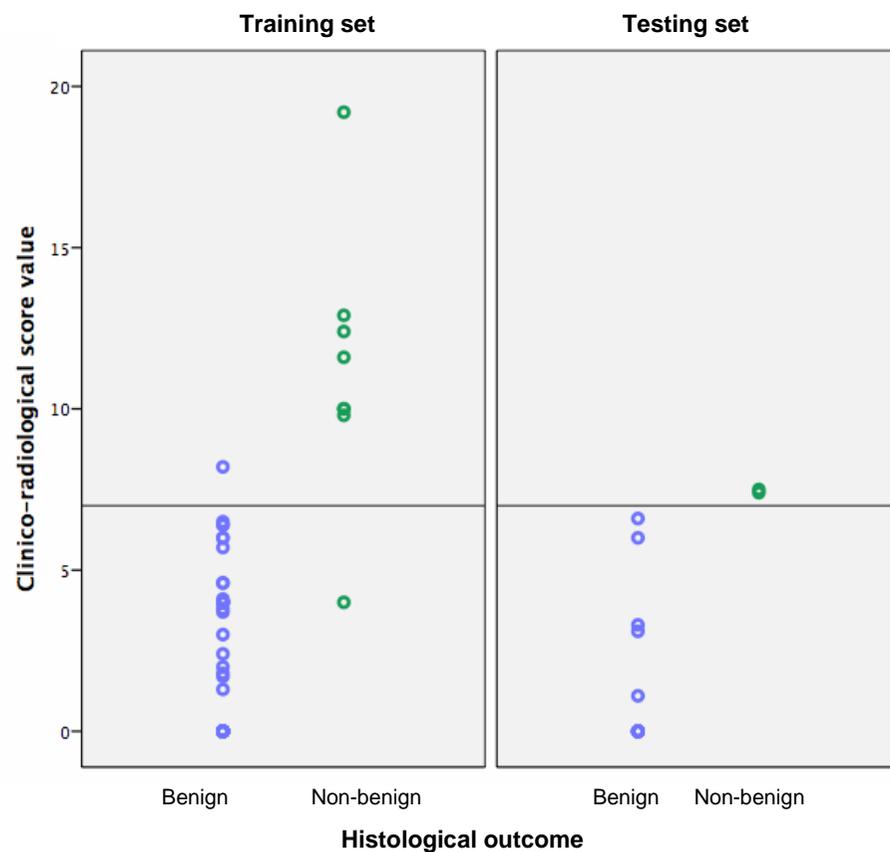
	NPV (%)	PPV (%)	Specificity (%)	Sensitivity (%)
Training set	97.9	87.5	97.9	87.5
Testing set	100.0	66.7	92.3	100.0

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Modelled outcomes for total data set at cutoffs:

Cutoff	NPV (%)	PPV (%)	Specificity (%)	Sensitivity (%)	False -ve	False +ve
≥ 5	98.1	50.0	85.0	90.0	1	9
≥ 6	98.1	52.9	86.7	90.0	1	8
≥ 7	**98.3**	**81.8**	**96.7**	**90.0**	**1**	**2**
≥ 8	95.2	87.5	98.3	70.0	3	1
≥ 8	95.2	100.0	100.0	70.0	3	0
≥ 9	93.8	100.0	100.0	60.0	4	0

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	Clinico-radiological score (Cutoff: ≥ 7)	Clinical score (Cutoff: ≥ 9)	Imaging score (Cutoff: ≥ 4)
Sex cord tumor with annular tubules	10.0	7.0	1.0
Cystic mucinous tumor, focal borderline change	10.0	13.0	4.0
Yolk sac tumor	7.5	7.0	4.0
Immature teratoma with yolk sac component	17.2	15.0	5.0
Immature teratoma grade 1	11.1	14.0	6.0
Yolk sac tumor (Endodermal sinus tumor)	10.5	14.0	6.0
Immature teratoma grade 2	11.6	14.0	5.0
Immature teratoma grade 1	8.3	14.0	6.0
Borderline mucinous tumor	4.0	8.0	5.0
Sertoli-Leydig cell tumor	7.4	12.0	3.0

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Discussion
Clinico-radiological score

Variable	Criteria	Points
Max diameter of largest solid component	(cm)	(value in cm)
Enhancement / flow in a septum / solid papillary projection	Present	4
Hormonal symptoms	Present	6
	Total points	

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Discussion

Clinico-radiological score: excluded variables

Variable	Criteria	Points
Max diameter of largest solid component	(cm)	(value in cm)
Enhancement / flow in a septum / solid papillary projection	Present	4
Hormonal symptoms	Present	6
Total points		

☒ Tumor markers

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Discussion
Clinico-radiological score: excluded variables

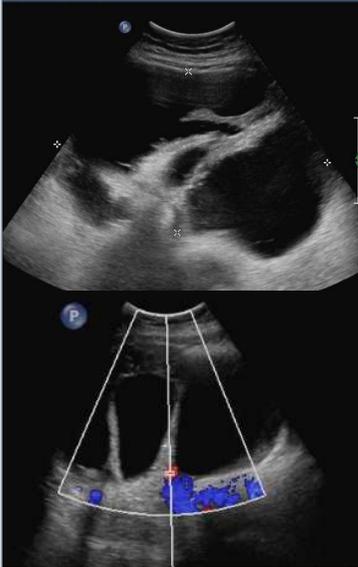| Variable	Criteria	Points
Max diameter of largest solid component	(cm)	(value in cm)
Enhancement / flow in a septum / solid papillary projection	Present	4
Hormonal symptom	Present	6
Total points		

☒ Tumor markers

☒ Absolute lesional size

Discussion
Study limitations

❖ **Small numbers**

❖ **Retrospective data**

- **Limit statistical strength**

- **Limit number of candidate variables**

» *Opt to include larger number & range of variables*

❖ **Established tests / features**

- **Mostly adult experience**

- **Exclude lesser-established markers**
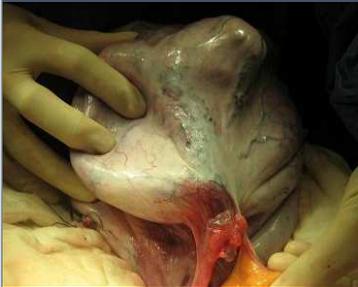
» *Pilot index: easily applicable & usable*

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Discussion

Future development

❖ **Impact on treatment outcomes**

- **Reduce understaging**
- **Reduce surgical morbidity**

❖ **Validate in other populations**

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Summary

❖ **Goal: Objective risk evaluation within limits of current modalities**

❖ **Result: Pediatric Risk of Malignancy Index**

Variable	Criteria	Points
Max diameter of largest solid component	(cm)	(value in cm)
Enhancement / flow in a septum / solid papillary projection	Present	4
Hormonal symptoms	Present	6
Total points		

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Acknowledgements

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Questions