REVIEW

Prognostic value of the Weiss and Wieneke (AFIP) scoring systems in pediatric ACC – a mini review

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Abstract

Histopathological differentiation in pediatric adrenocortical carcinoma (pACC) is difficult and clinical prediction and stratification scores are not evaluated yet. Therefore, this review aims to summarize current evidence on the value and accuracy of the two commonly used scoring systems (Weiss/Armed Forces Institute of Pathology (AFIP)) pACC. On this base, one might be able to evaluate if patients may benefit from a unique scoring system. For this, we performed a systematic review of the published literature and included 128 patients in our analysis. The majority (72%) of the pACCs had a good clinical course. The follow-up time ranged from 0 to 420 months with a mean age of 5.6 years at diagnosis. Patients with a good clinical course were younger (mean 4.8 years) than patients with a poor outcome (mean 7.6 years). Comparing the two scoring systems, the specificity of the Weiss score was very low (25%), whereas the sensitivity was 100%. According to the AFIP score, specificity (77%) was higher than the Weiss score, whereas the sensitivity of the AFIP score was minimal lower with 92%. Age differences were recognizable as the specificity was lower in infants <4 years (20%) than in older children (32%). In contrast, the specificity of the AFIP score was higher in infants <4 years (82%) than in older age groups (76%). Summarizing our results, we could show that the Weiss score is not a suitable tool for the prediction of malignancy in pACC in comparison with the AFIP score, but further efforts may seek to ensure early and accurate stratification through augmented scoring.

Key Words
- pediatric ACC
- Wieneke score
- Weiß score
- AFIP score
- pathologic scoring system

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Introduction

Pediatric adrenocortical carcinoma (pACC) is an extremely rare malignancy with an estimated incidence of 0.2–0.4 per million, accounting for approximately 0.2% of all childhood malignancies (Ribeiro *et al.* 2012, Kerkhofs *et al.* 2013). According to current evidence, there are significant differences in pathogenesis, clinical presentation, and prognosis between children and adults. This is especially pronounced in infants (<4 years) with

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pACC who present with a different hormone profile and seem to have a more favorable outcome (Mendonca *et al.* 1995, Riedmeier *et al.* 2021, Zambaiti *et al.* 2021). Several authors have discussed the hypothesis of adrenocortical tumor development in the fetal zone of the adrenal gland in early childhood (Dehner & Hill 2009, Lalli & Figueiredo 2015) – as already known for other pediatric tumors of the adrenal gland (Blavier *et al.* 2020).

Histopathological differentiation between benign and malignant adrenocortical tumor remains difficult, and clinical prediction and stratification scores are not evaluated yet in pediatric settings.

The Weiss histopathologic scoring system, intended and well established for the classification of adrenocortical neoplasms in adults, contains nine criteria: high nuclear grade (Führman G3/G4), >5 mitoses/50 HPF (equivalent to 10 mm²), abnormal rate of mitosis, <25% clear cells, >33% diffuse architecture, tumor necrosis, venous invasion, sinusoid invasion, and capsular invasion. According to the modified Weiss scoring system, tumors are classified as ACC if three or more criteria were present (Table 1) (Weiss 1984, Weiss *et al.* 1989). Discrepancies between Weiss scoring criteria and clinical outcome in terms of overestimation of biological aggressiveness have been frequently reported for pediatric patients (Wieneke *et al.* 2003, Chatterjee *et al.* 2015, Gupta *et al.* 2018, Jehangir *et al.* 2019).

In order to find an applicable classification system for pediatric patients, the Armed Forces Institute of Pathology (AFIP) score, widely known as Wieneke score, was developed nearly 20 years ago by modifying the Weiss criteria and complementing histopathological aspects. The following parameters were included: tumor weight >400 g, tumor size >10.5 cm, extension into periadrenal soft tissue and/or adjacent organs, invasion into the vena cava, venous invasion, capsular invasion, presence of tumor necrosis, mitotic index > 15/20 high-power fields (equivalent to 4 mm²), and presence of atypical figures. Ranging from 0 to 9 points, two or fewer points were classified as benign adrenocortical tumors, 3 points as intermediate for malignancy, and 4 or more points were designated as ACC (Table 1) (Wieneke *et al.* 2003).

The reliability of the AFIP scoring system in predicting malignancy in pACC has been confirmed by several authors (Wieneke *et al.* 2003, Magro *et al.* 2012, Dall'Igna *et al.* 2014, Chatterjee *et al.* 2015, Jehangir *et al.* 2019). However, as pediatric ACC are rare, the experiences with every single entity may be limited. Therefore, the aim of this review is to summarize current evidence on the value and accuracy of the two commonly used scoring systems – Weiss and AFIP – in pACC with the goal to identify if patients may benefit from a unique scoring system.

Methods

For our recent review, 'Adrenocortical Carcinoma in Childhood: A Systematic Review' (Riedmeier *et al.* 2021), PubMed and Embase databases were searched up to 15 February 2021 for manuscripts published after 1 January 1987. The search strategy for PubMed was as follows: ('child*'[Title/Abstract] OR 'pediatric*'[Title/Abstract]) AND ('cancer'[Title/Abstract] OR 'carcinoma'[Title/Abstract] OR 'tumor'[Title/Abstract] OR 'malign*'[Title/Abstract]) AND ('adrenocortical'[Title/Abstract] OR 'acc'[Title/Abstract] OR 'adrenal*'[Title/Abstract]). For Embase, we focused on the title and the abstract: AND ('adrenocortical' OR 'acc' OR 'adrenal*'). The first

Table 1 Criteria and classification of the two scoring systems for pediatric ACC: Wieneke score (AFIP) and Weiss score.

	AFIP score (Wieneke)	**Weiss score**
Criteria	Tumor weight > 400 g	High nuclear grade (Führman G3/G4)
	Tumor size > 10.5 cm	>5 mitosis/50 HPF
	Extension into periadrenal soft tissues and/or adjacent organs	Abnormal mitoses
	Invasion into vena cava	<25% clear cells
	Venous invasion	>33% diffuse architecture
	Capsular invasion	Tumor necrosis
	Presence of tumor necrosis	Venous invasion
	>15 mitoses per 20 HPF	Sinusoid invasion
	Presence of atypical mitotic figures	Capsular invasion
Classification		
	≤2 criteria = benign	≤2 criteria = benign
	3 criteria = intermediate for malignancy	
	≥4 criteria = malignant	≥3 criteria = malignant

AFIP, Armed Forces Institute of Pathology.

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inclusion criteria were the availability of English or German abstracts. For the current study, we used these results and expanded the search in PubMed for manuscripts including the term 'Wieneke' and/or 'AFIP' and 'adrenocortical', 'adrenal cortical', and 'adrenal cortical neoplasm' in order to detect manuscripts that were published after February 2021 and/or were not found by the recent search strategy. All relevant articles underwent full-text review to determine eligibility for inclusion in our analysis. In case of disagreement on the inclusion of manuscripts, it was discussed and resolved by consensus. The authors (MR, VW) separately confirmed excerpted data for inclusion. Eighteen articles were identified. After a full-text review, four published manuscripts were suitable for inclusion (Wieneke *et al.* 2003, Chatterjee *et al.* 2015, Jehangir *et al.* 2019, Paschoalin *et al.* 2022). Inclusion criteria were a minimum of three reported patients with confirmed histological ACC diagnosis, information regarding patient age (age <21 years), clinical outcome, and prognostic classification according to either or both AFIP and Weiss histopathological scoring system.

In total, 128 patients were included in the study. We extracted data of 33 patients from 2 publications – both retrospective reports (Chatterjee *et al.* 2015, Jehangir *et al.* 2019). To obtain more detailed information about the patients mentioned in two published manuscripts (Wieneke *et al.* 2003, Paschoalin *et al.* 2022), two of the authors, LDR Thompson and CAF Molina were contacted. Of these, we included data of 95 patients: 40 patients from Wieneke *et al.* (2003) and 55 patients from Paschoalin *et al.* (2022). Inclusion criteria for patients were availability of scoring number of AFIP and Weiss, age (<21 years) and follow-up data. In the case of data of Wieneke *et al.* (2003), we did not obtain the scoring points of the patients but the respective histopathologic criteria of each patient, and they were re-classified according to AFIP and Weiss criteria. The data obtained by Thompson and colleagues lacked two of the nine criteria for the classification of the Weiss score: high nuclear grade (Führman G3/G4) and <25% clear cells. Subsequently, although the data of 39 patients were included according to the Weiss score (maximum 7 instead of 9 points), it is possible that the score could be 2 points higher than calculated.

Results

The majority of patients with fully available datasets for the purpose of our review ($n = 92/128$; 72%) had a good clinical course described as alive with complete remission and no recurrence by computed tomography – according to their follow-up outcomes, whereas an unfavorable course – described as death from disease or alive with disease – was reported for less than a third of patients ($n = 36/128$; 28%) (Table 2 and more detailed Supplementary Table 1, see section on supplementary materials given at the end of this article). Of the patients with an adverse clinical course, most died due to ACC (31/36; 86%). Follow-up time ranged from 0 to 420 months. The follow-up data of patients with good (mean = 158 months) and poor (mean = 132 months) outcomes did not differ essentially.

The mean age at clinical presentation was 5.6 years (median ± S.D. 3 ± 5.3 years; range 0 months to 19 years), but most patients (55%) were infants (<4 years old), with 21% between 4 and 10 years old, and 24% older than 10 years. Of note, the mean age of the patients with a good clinical course was younger (4.8 years; 60% <4 years) than the mean age of patients with a poor outcome (7.6 years; 42% <4 years) (Table 2 and more detailed Supplementary Table 1).

Significantly, the specificity of the Weiss score was very low (25%): of patients with a good clinical course, only 25% were classified as benign adrenal cortical neoplasms according to the Weiss histopathological scoring system (<3 points), whereas the score yielded false positive results in 75% of patients (≥3 points). The Weiss score sensitivity was 100%, as all patients with poor clinical outcomes were classified as pACC (Table 3 and more detailed Supplementary Table 2).

According to the AFIP scoring system, specificity (77%) was higher than the Weiss score, as approximately three-quarters of patients with good clinical outcomes were classified as benign neoplasms. The sensitivity of the AFIP score was 92%: two children with a score of 3 points (intermediate for malignancy) developed aggressive pACC (Table 3 and more detailed Supplementary Table 2).

Furthermore, there were differences in specificity between the age groups for both scoring systems: the Weiss score specificity was lower in infants <4 years (20%) than in children older than 4 years (32%). By contrast, the specificity of the AFIP score was higher in infants <4 years (82%) than in older age groups (76%) (Table 3 and more detailed Supplementary Table 2).

Discussion

Pediatric tumors appear to have distinct features from histologically similar tumors in adults and pathologic

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Table 2 Descriptive data of 128 pediatric patients with good ($n = 92$) and bad ($n = 36$) clinical course of adrenocortical tumor of selected publications identified by systematic literature review: Age of patients (0–3; 4–19 years), number of patients (*n*), scoring points of AIFP and Weiss score, and respective number of patients of each scoring.

Author	Patients (*n*)	Clinical course	Patients (*n*)	Age (years)	Patients (*n*)	Scoring points	Weiss score (*n*)	Weiss score (%)	Scoring points	AFIP score (*n*)	AFIP score (%)
All patients	128	Good course	92	0–3	55	0	3	5	0	9	16
						1	3	5	1	9	16
						2	1	2	2	5	9
						3	9	16	3	4	7
						4	5	9	4	3	5
						5	6	11	5	0	0
						6	3	5	6	0	0
						7	0	0	7	0	0
						8	0	0	8	0	0
						9	0	0	9	0	0
						<3	4	7			
						≥3	21	38			
									<4	18	33
									≥4	7	13
						Median + Q,B,	3 ± 1.76			1 ± 1.3	
				4–19	37	0	1	3	0	7	19
						1	3	8	1	5	14
						2	2	5	2	3	8
						3	6	16	3	3	8
						4	5	14	4	0	0
						5	1	3	5	1	3
						6	3	8	6	2	5
						7	0	0	7	0	0
						8	1	3	8	1	3
						9	0	0	9	0	0
						<3	6	16			
						≥3	9	24			
									<4	10	27
									≥4	5	14
						Median + Q,B,	3 ± 1.9			1 ± 2.3	
		Bad course	36	0–3	15	0	0	0	0	0	0
						1	0	0	1	0	0
						2	0	0	2	0	0
						3	0	0	3	1	7
						4	1	7	4	2	13
						5	0	0	5	0	0
						6	1	7	6	3	20
						7	4	27	7	2	13
						8	2	13	8	0	0
						9	0	0	9	0	0
						<3	0	0			
						≥3	7	47			
									<4	1	7
									≥4	6	40
						Median + Q,B,	7 ± 1.19			6 ± 1.4	
				4–19	21	0	0	0	0	0	0
						1	0	0	1	0	0
						2	0	0	2	0	0
						3	0	0	3	1	5
						4	2	10	4	1	5
						5	4	19	5	3	14
						6	4	19	6	2	10
						7	2	10	7	4	19
						8	1	5	8	1	5
						9	0	0	9	1	5
						<3	0	0	<3		
						≥3	8	38	≥3		
						<4			<4	0	0
						≥4			≥4	8	38
						Median + Q,B,	6 ± 1.14			6 ± 1.59	

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criteria for malignancy of adult ACC – which are already well established – have not been reliable in malignancy prediction in pediatric patients. Accurate differentiation between benign and malignant pediatric adrenocortical neoplasms remains a challenge (Ribeiro *et al.* 1990, Michalkiewicz *et al.* 2004, Dehner & Hill 2009).

In order to identify patient groups that may benefit from a separate scoring system, we summarized previous research on the reliability of these two scoring systems. As reported in several studies, our study confirmed once again that the Weiss score is not a suitable tool for the prediction of malignancy in pACC because it lacks accuracy. Although the sensitivity is high (100%), the Weiss score leads to an overestimation of malignancy with low specificity (25%) which means that only one in four children with a benign clinical course was classified as benign. To avoid unnecessary treatment and psychological stress for patients and their families, this scoring system clearly should not be used to classify pACC. Compared to the Weiss system, AFIP scoring achieved much more reliable results with a specificity of 76% and a sensitivity of 94%. AFIP scoring is currently the most suitable and most reliable histopathological scoring system, although there are still limitations in accuracy and predictive value.

Our novel finding is the dependency on patient age when looking at the reliability of the two scoring systems. While the specificity of Weiss scoring was even lower for infants under 4 years of age, the AFIP scoring showed slightly more accurate results for infants (<4 years) than for older children. As younger patients seem to have a better diagnosis than older children and adults, one hypothesis could be a different origin of the cancer cells. Several authors postulate a fetal zone-derived tumorigenesis in early childhood (Dehner & Hill 2009, Lalli & Figueiredo 2015) – as known for other pediatric adrenal tumors (Blavier *et al.* 2020). We, therefore, recommend that age should be taken into account for clinical risk stratification while infants (up to 4 years) may benefit from a separate scoring system.

To draw conclusions about the reasons for the age-dependent accuracy of these two scoring systems, we analyzed the singular factors of 97 patients from Wieneke *et al.* (2003) and Paschoalin *et al.* (2022) from four different age groups. No relevant age-related differences were found for factors represented in both scoring systems. Factors that were only present in the Weiss scoring system appeared to be more relevant to the pACC of infants and prepubertal children. In particular, factors such as high nuclear grade (Führman G3/G4) and mitotic rate appeared to be more important in infant pACC. This could be an explanation for the low specificity of Weiss scoring especially for infants. On the other hand, the decrease in mitotic rate with age could also lead to a lower sensitivity of AFIP scoring in older children and adults. In addition, it should be noted that, apart from mitotic rate, factors that were only included in the AFIP scoring system (e.g. tumor weight, tumor size, etc.) were more frequently positive in adult ACCs.

This review has several limitations especially as included data are retrospective, patient groups are heterogeneous, with specimens classified by different pathologists. In addition, two scoring points of Thompson's data for the Weiss scoring system were

Table 3 Specificity and sensitivity of Weiss and AFIP scoring in pACC. Comparison of sensitivity and specificity of the scoring systems Weiss and AFIP for 128 pediatric patients with a good and bad clinical course of adrenocortical tumor of selected publications identified by systematic literature review: age groups (all; 0–3; 4–19 years), number of patients (*n*), true negative/false negative/true positive, and false positive results.

Scoring system	**Age** (in years)	***n***		**True negative**	**False negative**	**True positive**	**False positive**	**Specificity**		**Sensitivity**	
Weiss	All	128	*n*	23	0	36	69				
			%	18%	0%	28%	54%	25%		100%	
AFIP			*n*	63	3	33	19				
			%	49%	2%	26%	15%	77%	***P* = 0.002**	92%	*P* = 0.12
Weiss	0–3	70	*n*	11	0	15	44				
			%	16%	0%	21%	63%	20%		100%	
AFIP			*n*	45	2	13	10				
			%	64%	3%	19%	14%	82%	***P* = 0.001**	87%	*P* = 0.21
Weiss	4–19	58	*n*	12	0	21	25				
			%	21%	0%	36%	43%	32%		100%	
AFIP			*n*	28	1	20	9				
			%	48%	2%	34%	16%	76%	*P* = 0.08	95%	*P* = 0.39

Significant *P* values are bold.

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not included, potentially underscoring the tumors. To minimize this risk of bias, we made a subgroup analysis comparing all except Thompson's data. The results show that there is no relevant difference between the two groups (Supplementary Table 3). Surprisingly, the specificity of the Weiss score of Thompson's data is even lower than that of the other data although it would have been expected otherwise. As the follow-up time of patients with good outcome was slightly lower than the follow-up time of patients with bad outcomes, there might be a small bias because poor outcomes may be diagnosed later.

In summary, it should be emphasized that both scores lack overall reliable risk stratification. To achieve successful stratification, additional criteria such as age, further pathological factors such as Ki67 proliferation index, and potentially even genetic evaluation (genomics, transcriptomics, proteomics) may be needed to augment the AFIP scoring system. Such a stratification has already been achieved for other solid tumors in childhood, for example N-MYC and *p1*-deletion in neuroblastoma (Attiyeh *et al.* 2005, Pinto *et al.* 2015) and WNT alterations and molecular classification in medulloblastoma (Taylor *et al.* 2012, Ramaswamy *et al.* 2016). In the field of adult ACCs, there are already attempts to establish diagnosis-related and therapy-relevant stratification scores using S-GRAS scoring system, which takes into account various clinical and pathological factors (Elhassan *et al.* 2021). In the short term, the AFIP scoring system using pathological criteria is a useful guide for risk stratification of pACC, but further efforts may seek to ensure early and accurate diagnosis and stratification through augmented scoring.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/ERC-22-0259.

Declaration of interest

There are no conflict of interest to declare. All authors have read and approved this manuscript.

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