The discordance analysis characteristics (DAC) approach - a novel method to investigate the relationships of patient's properties and accuracy of different diagnostic tests

Keller T[1], Butz H[2], Jung K[3]
[1]*ACOMED statistik, Leipzig, Germany*
[2]*Bayer Vital GmbH, Fernwald, Germany*
[3]*Department of Urology, University Hospital Charité, Humboldt University Berlin, Berlin, Germany*

Introduction Accuracy of diagnostic tests in clinical chemistry is usually compared via areas under curves (AUC) of receiver operating characteristics or sensitivities (specificities) at given specificities (sensitivities), respectively. Strongly correlating diagnostic tests (e.g. in case of subforms of a molecule) are often compared using subgroups chosen by ranges of the reference test. It has been shown [1] that this procedure is biased. Using the method of discordance analyis characteristics [1] these biases can be avoided. According to this method, test results of discordantly tested patients (true and false positives or corresponding negatives: TP, FP, TN, FN) are compared over the whole range of sample population or over a selected or given range of cut off values. The method leads to similar results as ROC analysis, but subgroups like e.g. greyzone patients, can be analysed without biases. In this contribution, the method is enlarged in a way, that not only test results but also properties like e.g. age, stage of discordantly tested patients are compared via DAC method. The method is demonstrated by the example of the two tumor markers, total and complexed prostate specific antigen (tPSA and cPSA) which are used for diagnosis of prostate cancer (PCa). Age, prostate volume and staging (Gleason score) of discordantly tested patients are compared in dependence on test result and disease.

Material and Methods: *DAC-Method:* (step a) At a study population, all cut-off pairs $c_{i,j}$ (i: number of cut-off pairs within the interesting range, $i \in (1, \ldots, N)$; j: tests, $j \in (1,2)$) are determined using a prospectively fixed criterion (here: same sensitivity). (step b) Test results ($TP_{i,j}$, $FP_{i,j}$, $TN_{i,j}$, $FN_{i,j}$) of discordantly tested patients are identified and counted for all cut off pairs. (step c) Using these numbers, sensitivity- and specificity-like parameters can be calculated (here: only DAC-specificity). Furthermore, predictive values within discordantly tested patients can be estimated. (step d) Medians of parameters described in step c are calculated within interesting range. Using bootstrapping, confidence intervals of DAC-specificities can be estimated whereby non-overlapping indicates significant difference.

Enlargement of DAC method to patient's properties: The same procedure is used, but instead of counts of test results and related parameters medians of patient's properties are calculated and used for further analysis.

Patients and laboratory method: For elaboration of the DAC method, we used the tPSA and cPSA data from a diagnostic study to compare diagnostic accuracy of PSA forms in case finding situation [study B in 2]. Details concerning the study groups, blood sample collection and storage, and analytical methods were given in the original reports [2, 3]. Briefly, the study included 924 men. A total of 565 patients were diagnosed as having prostate cancer (PCa), whereas in 359 men no evidence of prostate cancer (non-PCa) was found in prostate biopsies. PSA concentrations were measured by the Bayer Immuno 1 PSA and cPSA assays (Bayer Diagnostics) as described previously [3].

Results: Medians of DAC-specificities of 0.85 (95% CI: 0.78 – 0.92) for patients positively tested by cPSA (negatively by tPSA) and 0.15 (95% CI: 0.08-0.22) for patients positively tested by tPSA (negatively by cPSA) were estimated. Areas under the whole ROC curve were 0.709 (0.678–0.738) for cPSA and 0.683 (0.652–0.713) for tPSA, respectively ($p<0.001$). Analysing a cut-off range described by tPSA (3 – 5 µg/L) and – based on identical sensitivities - cPSA (2.6 - 4.3 µg/L) an elevated DAC-specificity is demonstrated for cPSA compared with tPSA (0.93 (95% CI: 0.87-1.00) vs. 0.07 (95% CI: 0.00-0.13)).

Related to their properties, patients with prostate cancer who have been positively tested by cPSA and negatively tested by tPSA are significantly younger and have significantly smaller prostate volumes (Tab. 1). No difference in Gleason score has been found. For patients with benign prostate diseases, age of false positive detected patients does not differ between both groups of discordantly tested patients, whereas prostate volume is larger among patients tested positively with tPSA (Tab. 1).

	age [years]		prostate volume [cm^3]		Gleason score	
PCa (tPSA+, cPSA-)	65.3 (62.8 - 67.4)	*	44.0 (36.7 - 50.5)	*	6.3 (6.0 - 6.6)	-
PCa (tPSA-, cPSA+)	61.0 (58.7 - 63.0)		30.3 (27.7 - 33.4)		6.4 (6.0 - 6.7)	
non-PCa (tPSA+, cPSA-)	69.0 (66.2 - 71.2)	-	69.5 (60.4 - 77.8)	*	not available for benign diseases	
non-PCa (tPSA-, cPSA+)	69.0 (63.0 - 75.0)		28.0 (23.0 - 46.3)			

Tab. 1 DAC-results for age, tumour volume and Gleason score for cut off range tPSA (3 – 5 µg/L) and cPSA (2.6 - 4.3 µg/L): median (95%-CI) * non overlapping of confidence intervals indicates significant difference

Discussion: The recently introduced DAC method is an interesting alternative method to ROC analysis when two strongly correlating diagnostic tests should be compared. Especially in case of subgroup analysis regarding diagnostic grey zones, biases can be avoided by using DAC-method. Shown by the example of comparison of diagnostic accuracy of cPSA and tPSA, significant reduced number of false positives was found for cPSA leading to a reduced number of unnecessary biopsies in clinical practice. The extend application of the DAC method to patient's properties allows new insight into relationships of diagnostic accuracy and patient's characteristics which is not possible in that direct manner when ROC analysis is used. Especially the graphs of DAC-related diagnostic accuracy parameters and patient properties use similar design and allow direct visualisation of relationships.

Demonstrated by the example of PCa diagnosis using the tumor markers cPSA and tPSA it can be shown, that in case of discordant test results cPSA detects younger PCa-patients with smaller prostate volumes in comparison to tPSA which detects older PCa-patients with higher volumes. These findings correspond to pathophysiological understanding and experience. These results are of clinical significance since younger patients with small prostate volume are often non-symptomatic patients in contrast to older patients with enlarged prostate volumes and furthermore younger PCa-patients would profit the most from early curative therapy.

Literatur

[1] Keller T, Butz H, Lein M, Kwiatowski M, Semjonow A, Luboldt H-J, Hammerer P, Stephan C, Jung K: Discordance Analysis Characteristics (DAC) as a New Method to Compare the Diagnostic Accuracy of Tests: the Example of Complexed Versus Total Prostate-Specific Antigen. Clin Chem 2005, 51, 532-539.

[2] Jung K, Lein M, Butz H, Stephan C, Loening SA, Keller T: New Insights into the Diagnostic Accuracy of Complexed and Total Prostate Specific Antigen Using Discordance Analysis Characteristics. Urology 175 (4) 1275-1280 (2006).

[3] Lein M, Kwiatkowski M, Semjonow A, Luboldt H-J, Hammerer P, Stephan C, et al. A multicenter clinical trial on the use of complexed prostate specific antigen in low prostate specific antigen concentrations. J Urol 2003;170:1175–9