Second line tests in the differential diagnosis of neoplastic and non-neoplastic hypercortisolism: a systematic review and meta-analysis

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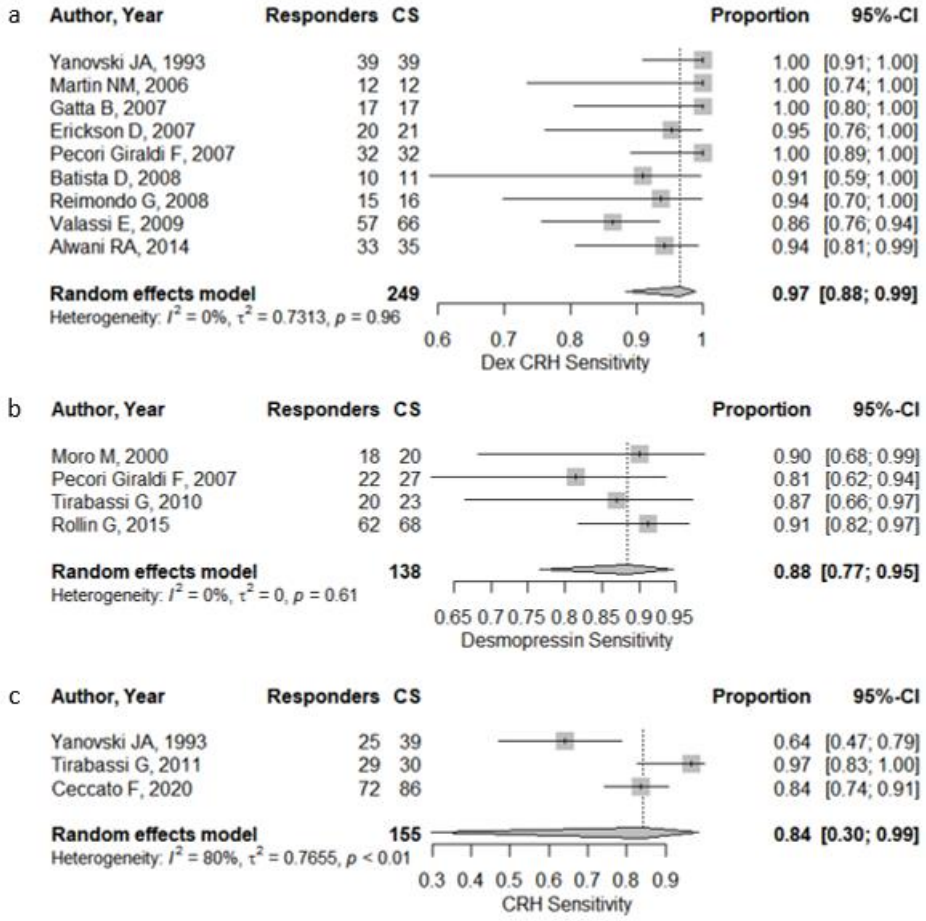
Supplementary data

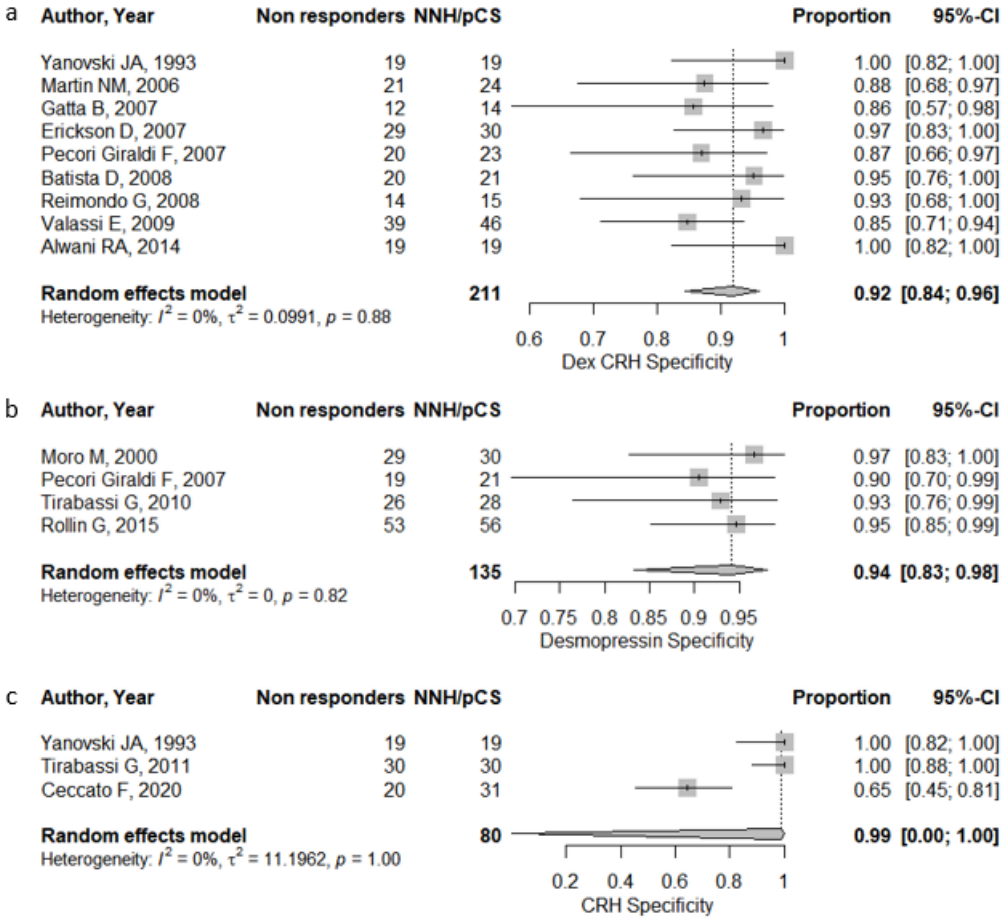
Supplementary table 1. Protocol for the application of QUADAS-2 tool. Every item is evaluated for risk of bias and applicability concern, except the latter: flow and timing item was assessed only for the risk of bias domain.

<table>
<tr><td colspan="2">1) Patient selection</td></tr>
<tr><td>Risk of bias</td><td>Applicability concern</td></tr>
<tr><td>Low risk of bias was attributed to complete and consecutive series without post-hoc inappropriate exclusion of patients. Concerns regarded random or incomplete inclusions or inappropriate exclusions of patients. In the presence of both the concerns above, the study was deemed at high risk of bias.</td><td>Low applicability concern was attributed to studies including only patients presenting clear pCS-related conditions in the control group. Concerns rose when the study also included CS-excluded patients in the NNH/pCS group. When the number of CS-excluded patients exceeded that of patients presenting pCS-related conditions the applicability concern was deemed high.</td></tr>
<tr><td colspan="2">2) Index test</td></tr>
<tr><td>Risk of bias</td><td>Applicability concern</td></tr>
<tr><td>Studies prospectively designed with predefined threshold presented a low risk of bias. Some concerns were addressed for ROC-based thresholds or in case of a retrospective design. High risk of bias was addressed for retrospective studies using a ROC-based threshold.</td><td>Researchers evaluated whether the index tests (and their protocol and interpretation) matched the review question and provided the grading accordingly (low/ some concerns/ high).</td></tr>
<tr><td colspan="2">3) Reference standard</td></tr>
<tr><td>Risk of bias</td><td>Applicability concern</td></tr>
<tr><td>Low risk of bias was assessed for studies providing histological confirmation of CS or in case of hypercortisolism remission after surgery. Some concerns rose for studies including patients with persistence after surgery and without histological confirmation. High risk of bias was attributed to studies with CS diagnosis based on progressing clinical or biochemical features.</td><td>Low concern was addressed for studies including only CD patients presenting mild to moderate hypercortisolism. In case of studies including non-pituitary CS (i.e., EAS, ACES) and/or CD patients with severe hypercortisolism researchers could rise some concerns or decide for a high concern judgement.</td></tr>
<tr><td colspan="2">4) Flow and timing</td></tr>
<tr><td colspan="2">Risk of bias</td></tr>
<tr><td colspan="2">Low risk of bias was assigned to studies with at least one year of follow-up to define NNH/pCS patients and with index tests applied prior to reference standard for CS patients. Some concerns rose in case of CS patients receiving the index tests after the reference standard and/or in case of short follow-up for defining NNH/pCS (i.e., < 1 year). If these patients were the majority of the population studied, a high risk of bias was attributed to the study.</td></tr>
</table>

Supplementary figure 1. Pooled effects for sensitivity of Dex-CRH test (a), Desmopressin test (b) and CRH test (c). CS = Cushing's syndrome; Dex = dexamethasone; CRH = corticotropin realising hormone; CI = confidence interval.



Supplementary figure 2. Pooled effect for specificity of Dex-CRH test (a), Desmopressin test (b) and CRH test (c). NNH/pCS = non-neoplastic hypercortisolism/pseudo-Cushing; Dex = dexamethasone; CRH = corticotropin realising hormone; CI = confidence interval.



Supplementary figure 3. Funnel plot analysis for Dex-CRH test (a), Desmopressin test (b) and CRH test (c). Dex = dexamethasone; CRH = corticotropin realising hormone.