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REVIEW ARTICLE

NEXUS vs. Canadian C-Spine Rule (CCR) in Predicting Cervical Spine Injuries; a Systematic Review and Meta-analysis

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Abstract: **Introduction:** Clinical decision tools have been shown to reduce imaging rates for clearance of suspected cervical spine injury (CSI). This review provides more comprehensive evidence on the diagnostic capabilities of National Emergency X-Radiography Utilization Study (NEXUS) and Canadian C-spine rule (CCR) in this regard. **Methods:** A systematic review of the current literature was performed on studies published until Jan 26^{th}, 2023, in databases of Medline, Scopus, Web of Science, and Embase, investigating the performance of NEXUS and CCR in blunt trauma patients. QUADAS-2 and GRADE guidelines were used to assess the quality and certainty of evidence. All analyses were performed using the STATA 14.0 statistical analysis software. **Results:** 35 articles comprising 70000 patients for NEXUS and 33000 patients for CCR were included in this review. NEXUS and CCR were evaluated to have a sensitivity of 0.94 (95% confidence interval (CI): 0.88 to 0.98) and 1.00 (95% CI: 0.98 to 1.00) in the detection of any CSI and 0.95 (95% CI: 0.89 to 0.98) and 1.00 (95% CI: 0.95 to 1.00) in the detection of clinically important CSI. The area under the curve (AUC) of NEXUS and CCR was 0.85 and 0.97 for any CSI and 0.78 (95% CI: 0.74 to 0.81) and 0.94 (95% CI: 0.91 to 0.96) for clinically important CSI. **Conclusion:** Our study demonstrates that both NEXUS and CCR can be used in ruling out patients with low risk of CSI, and CCR was shown to have superior performance. Even though these tools have low specificity, their application can still greatly reduce the number of radiographic imaging performed in emergency departments.

Keywords: Spinal injuries; Diagnosis; Accuracy; Clinical decision rules

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1. Introduction

Cervical spine injuries (CSI) can lead to long-term injuries and disabilities and impose a heavy burden on the patient and healthcare system (1). Due to the importance of CSIs and the devastating consequences of undiagnosed clinically important injuries, most suspected CSI patients undergo radiographic imaging (2). However, clinically important CSI is observed in less than 3% of trauma patients, and cervical imaging evaluations are not necessary for all suspected CSI patients (3).

Several clinical decision tools and criteria have been proposed for the clearance of suspected CSI patients. These decision tools consist of a combination of patient history, physical examination findings, and injury mechanism and have been shown to reduce imaging rates by as much as 40% (4, 5). The application of such tools can aid physicians in ruling out patients with a low risk of CSI while reducing emergency department (ED) costs and avoidable radiation exposure (6).

National Emergency X-Radiography Utilization Study (NEXUS) (7) and Canadian C-spine rule (CCR) (8) are the two more widely used decision tools for the clearance of CSIs. NEXUS criteria consider posterior midline c-spine tenderness, intoxication, state of alertness, focal neurologic deficits, and distracting injuries. CCR includes assessment

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of patient age, injury mechanism, paresthesia in extremities, patient position and ambulation, assessment of neck range of motion, neck pain, and midline cervical spine tenderness. Suspected CSI patients undergo radiologic imaging if they fail any criteria of either decision tool. CCR and NEXUS have been shown to have sensitivities ranging from 80 to 100% (4), and guidelines have encouraged the use of such scores in clinical decision-making for trauma patients (9, 10).

The previously published systematic reviews and meta-analyses investigating the performance of NEXUS and CCR in detection of CSI in suspected CSI patients have demonstrated a possible clinical use for these tools. However, these studies have mostly investigated a specific age group and are limited by the scarce number of included articles and lack of direct assessments of NEXUS and CCR.

Moreover, most reviews are outdated (4, 11-13). This review updates the existing literature and provides more comprehensive evidence on the diagnostic capabilities of NEXUS and CCR in detection of CSI in suspected patients.

2. Methods

2.1. Study design and search strategy

This systematic review and meta-analysis was designed to evaluate the performance of NEXUS and CCR criteria in ruling out CSI in suspected CSI blunt trauma patients. PICO was defined as P: suspected CSI blunt trauma patients, I: NEXUS and/or CCR criteria, C: radiographic imaging, O: patients having CSI. Keywords related to "cervical spine injury", "National Emergency X-Radiography Utilization Study", and "Canadian C-spine Rule" were selected based on MeSH and Emtree terms of Medline and Embase databases, consultations with experts in the field, and a review of related literature. A systematic search was performed in online databases of Medline, Embase, Web of Science, and Scopus until Jan, 26th, 2023 (supplementary table 1). Manual search in Google and Google Scholar search engines and reference tracking were also performed to retrieve possibly missed articles.

2.2. Selection criteria

All studies assessing the performance of NEXUS and CCR criteria in ruling out CSI in blunt trauma patients, regardless of age, injury mechanism, and injury severity, were included. Studies without a non-CSI group or not reporting the required data, reviews, letters, editorials, and duplicate reports were excluded. The study with the largest sample size was selected among the studies performed on the same population with identical study conduction time periods.

2.3. Data extraction

Two investigators independently reviewed all retrieved records, and relevant articles were chosen through primary (title and abstract) and secondary (full-text) screening. The included articles and their reported data were summarized in a checklist designed according to preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (14). The information on study characteristics (first author, year, country, design), as well as patient setting, injury severity, outcome definition, utilized decision tool, sample size, and number of males were extracted. The reported data were gathered as true positive (TP), false positive (FP), true negative (TN), and false negative (FN). These values were calculated from the reported sensitivity and specificity when required.

2.4. Definitions

NEXUS and CCR were defined as originally designed by Hoffman et al. (7) and Stiell et al. (8), respectively. Clinically significant CSI was defined as proposed by Hoffman et al. (2) and Stiell et al. (15). In summary, CSI was considered clinically important except for isolated spinous process, transverse process, avulsion, and osteophyte fracture, and simple compression fractures involving less than 25% of the vertebral body height. Type 1 odontoid fracture, end plate fracture, and trabecular bone injury were also considered insignificant CSI. Geriatric patient was defined as $\geq$ 65 years, and pediatric patient was defined as < 18 years.

2.5. Quality assessment and certainty of evidence

The quality of the included articles was judged using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) guidelines (16). According to these guidelines, the risk of bias and applicability of studies are assessed in patient selection, study design, blind assessment of index text and reference standard, verification bias, and missing data. The Grades of Recommendation, Assessment, Development and Evaluation (GRADE) instructions (17) were used to evaluate the certainty of evidence. A third reviewer settled any disagreements throughout the investigations.

2.6. Statistical analysis

All analyses were performed using the STATA 14.0 statistical analysis software using the "midas" package. TP, FP, TN, and FN were used to calculate the summary receiver operating characteristic (SROC) curve, sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR). Additional analysis was performed according to patient age groups (adult, pediatric, geriatric). Sensitivity analysis was performed to assess the robustness of the results by providing analysis for studies with simultaneous assessment of NEXUS and CCR (direct assessment) and studies with outcomes of clinically important CSIs. Deek's funnel plot asymmetry test was used to evaluate publication bias.

3. Results

3.1. Study selection

The systematic search yielded 538 non-duplicate records, and 10 studies were retrieved via manual search. After primary and secondary screening, 35 articles were included in this review (Figure 1) (6-8, 18-49). All included articles were designed as observational (cross-sectional and cohort) studies. Characteristics of the included studies are provided in more detail in Table 1 and their respective sections.

3.2. Performance of NEXUS and CCR in detection of any CSI

Twenty-six articles comprising 69957 blunt trauma patients [2504 (3.57%) any CSIs], assessed the diagnostic accuracy of NEXUS (6, 7, 18-28, 30-34, 36-39, 41, 44, 48, 49). The area under the curve (AUC) of NEXUS for detection of any CSI was calculated as 0.85 (95% confidence interval (CI): 0.81 to 0.87) (Figure 2) with a sensitivity and specificity of 0.94 (95% CI: 0.91 to 0.97) and 0.32 (95% CI: 0.22 to 0.44), respectively. NEXUS criteria had a PLR of 1.4 (95% CI: 1.2 to 1.6) and NLR of 0.17 (95% CI: 0.10 to 0.29). The DOR of NEXUS was calculated as 7.96 (95% CI: 4.35 to 14.58) (Figure 3).

Seventeen articles comprising 33142 blunt trauma patients [1170 (3.53%) any CSIs], assessed the diagnostic accuracy of CCR (6, 8, 18, 24, 25, 28, 31, 32, 35, 37-42, 45, 47). CCR was shown to have an AUC of 0.97 (95% CI: 0.96 to 0.98) (Figure 2), and sensitivity and specificity of 1.00 (95% CI: 0.98 to 1.00) and 0.34 (95% CI: 0.20 to 0.51), respectively. CCR had a PLR of 1.5 (95% CI: 1.2 to 1.9) and NLR of 0.01 (95% CI: 0.00 to 0.05). The DOR of CCR for detection of any CSI was 185 (95% CI: 27 to 1252) (Figure 4).

Table 2 demonstrates the performance values of NEXUS and CCR in detection of any CSI.

3.3. Performance of NEXUS and CCR in the detection of any CSI in adult patients

Nineteen studies comprising 65862 patients (2045, [3.10%] CSI) evaluated the value of NEUXS in the detection of any CSI in adult patients (6, 18, 20, 22-24, 26-34, 36, 41, 43, 44). NEXUS was shown to have an AUC of 0.77 (95% CI: 0.73 to 0.81) (Supplementary Figure 1) with a sensitivity and specificity of 0.94 (95% CI: 0.88 to 0.98) and 0.27 (95% CI: 0.16 to 0.43), respectively. NEXUS had a PLR of 1.3 (95% CI: 1.1 to 1.5), NLR of 0.20 (95% CI 0.10 to 0.42) and DOR of 6 (95% CI: 3 to 14) (Supplementary Figure 2).

Thirteen studies comprising 30734 patients (793 [2.58%] CSI) evaluated the value of CCR in detection of any CSI in adult patients (6, 8, 18, 24, 28, 31, 32, 35, 40-42, 45, 47). CCR was shown to have an AUC of 0.91 (95% CI: 0.88 to 0.93) (Supplementary Figure 1) with a sensitivity and specificity of 1.00 (95% CI: 0.96 to 1.00) and 0.30 (95% CI: 0.17 to 0.49), respectively. CCR had a PLR of 1.4 (95% CI: 1.1 to 1.8), NLR of 0.01 (95% CI: 0.00 to 0.12) and DOR of 149 (95% CI: 13 to 1756) (Supplementary Figure 3).

3.4. Performance of NEXUS in detection of any CSI in geriatric patients

All geriatric patients should undergo radiographic imaging according to CCR, and no studies have assessed the value of CCR in detection of CSI in geriatric patients.

Eight studies evaluated the value of NEXUS in detection of any CSI in geriatric patients [7972 patients, 516 (6.47%) CSIs] (6, 22, 26, 27, 29, 33, 43, 44). NEXUS was shown to have an AUC of 0.66 (95% CI: 0.61 to 0.70) (Supplementary Figure 4) with a sensitivity and specificity of 0.97 (95% CI: 0.76 to 1.00) and 0.30 (0.17 to 0.48), respectively. NEXUS had a PLR of 1.4 (95% CI: 1.1 to 1.8) and NLR of 0.10 (95% CI: 0.01 to 1.03). The overall DOR for NEXUS was 14.36 (95% CI: 1.18 to 175.20) (Supplementary Figure 5).

3.5. Performance of NEXUS and CCR in detection of any CSI in pediatric patients

Five studies investigated the value of NEXUS in detection of any CSI in pediatric patients, comprising 4757 patients with 105 (2.20%) CSI cases (25, 37, 38, 46, 49). Our analysis showed an AUC of 0.64 (95% CI: 0.59 to 0.68) (Supplementary Figure 4), sensitivity of 0.98 (95% CI: 0.67 to 1.00) and specificity of 0.37 (95% CI: 0.24 to 0.51) for NEXUS. The PLR was 1.6 (95% CI: 1.3 to 1.9), and NLR was 0.04 (0.00 to 1.24). The overall DOR was calculated as 35 (95% CI: 1 to 10.58) (Supplementary Figure 6).

Three studies evaluated the value of CCR in detection of any CSI in pediatric patients (1400 patients, 16 CSI) (25, 37, 38). The studies reported sensitivities ranging from 85.71 to 100% and specificities ranging from 14.71 to 53.76%. No meta-analysis was performed due to the scarcity of included studies.

3.6. Sensitivity analysis

- Direct assessments of NEXUS and CCR in detection of any CSI

Thirteen studies had direct evaluations of the performance of NEXUS and CCR in detection of any CSI comprising 26484 patients [1109 (4.1%) CSIs] for NEXUS and 26073 patients [1104 (4.23%) CSIs] for CCR (6, 8, 18, 23-25, 28, 31, 32, 37-39, 41). Dickinson et al. (23) (utilizing NEXUS) and Stiell et al. (8) (utilizing CCR) included identical patients investigated in the same time period and were included in the analysis as direct comparisons. Our analysis demonstrated an AUC of 0.80 (95% CI: 0.76 to 0.83) for NEXUS and 0.96 (95% CI: 0.94 to 0.98) for CCR (Supplementary Figure 7). The sensitivity and specificity were calculated as 0.91 (95% CI: 0.86 to 0.95) and 0.36 (0.28 to 0.46) for NEXUS and 1.00 (95% CI: 0.98 to

1.00) and 0.27 (0.13 to 0.48) for CCR, respectively. The PLR and NLR were 1.4 (95% CI: 1.3 to 1.6) and 0.24 (95% CI: 0.15 to 0.38) for NEXUS and 1.4 (95% CI: 1.1 to 1.8) and 0.01 (95% CI: 0.00 to 0.08) for CCR, respectively. The overall DOR was 5.98 (95% CI: 3.49 to 10.23) for NEXUS and 123.42 (95% CI: 16.22 to 939.37) for CCR (Table 2) (Supplementary Figures 8 and 9).

- Performance of NEXUS and CCR in detection of clinically important CSI

Twelve articles evaluated the value of NEXUS criteria in detection of clinically important CSIs [55565 patients, 1084 (1.95%) CSIs] (7, 21-23, 25, 28, 34, 36-38, 41, 44). Our analysis demonstrated an AUC of 0.78 (95% CI: 0.74 to 0.81) (Figure 2), with sensitivity and specificity of 0.95 (95% CI: 0.89 to 0.98) and 0.41 (95% CI: 0.31 to 0.52), respectively. NEXUS criteria had a PLR of 1.6 (95% CI: 1.4 to 1.9) and NLR of 0.13 (95% CI: 0.07 to 0.25). The DOR of NEXUS was calculated as 12.25 (95% CI: 6.21 to 24.16) (Figure 5). Ten studies investigated the value of CCR in detection of clinically important CSIs [24074 patients, 448 (1.86%) CSIs] (8, 25, 28, 35, 37, 38, 40-42, 45). The AUC of CCR was calculated as 0.94 (95% CI: 0.91 to 0.96) (Figure 2) with a sensitivity and specificity of 1.00 (95% CI: 0.95 to 1.00) and 0.37 (95% CI: 0.25 to 0.52), respectively. CCR had a PLR of 1.6 (95% CI: 1.3 to 2.0) and NLR of 0.01 (95% CI: 0.00 to 0.14). The DOR of CCR was 235.59 (95% CI: 10.67 to 5201.97) (Figure 6). Table 2 demonstrates the validity indices of NEXUS and CCR in detection of clinically important CSIs.

3.7. Quality assessment and publication bias, critical appraisal of methodological bias

The quality of the included articles was assessed using QUADAS-2 guidelines. In the domain of patient selection, 10 studies were rated as unclear due to unclear sampling method (8, 20, 23, 24, 29, 35, 47, 48) and unclear exclusion criteria (19, 39). Eight studies were rated as having a high risk of bias in patient selection due to convenience sampling (28, 31-33, 36, 42, 44, 45). Twelve studies were unclear in their risk of bias of index test due to unclear index test assessor blinding (6, 19-21, 27, 29, 30, 32, 34, 40, 48, 49), and one study was rated as high due to no blinding of index test assessor (26). Eighteen studies had no mentions of reference standard assessor blinding and were rated as unclear in risk of bias of reference standard (19-22, 24, 27, 29, 33, 34, 36-40, 44, 46-49), and two studies were rated as high-risk due to no blinding (26) and inappropriate reference standard modality (35). Three studies were rated as unclear in the domain of flow and timing (36, 37, 48). Six studies utilized a modified index test and were rated as high-risk in the application of the index test (24, 31, 32, 44, 45, 49) (Table 3).

No publication bias was observed among the included studies investigating the performance of NEXUS (p = 0.57) and CCR (p = 0.36) in detection of any CSI. (Supplementary Figure 10).

No publication bias was observed among the included studies investigating the performance of NEXUS (p = 0.10) in detection of clinically important CSIs. Included studies investigating the performance of CCR in detection of clinically important CSI had publication bias (p = 0.02) (Supplementary Figure 10).

3.8. Certainty of evidence

According to GRADE guidelines, the base level of evidence was set as low since all included articles were observational studies. The certainty of evidence for the value of NEXUS was reduced by two, due to the risk of bias and heterogeneity in the included studies and increased by two, due to the very large magnitude of effect. Overall, the certainty of evidence for the value of NEXUS in detection of any CSI and clinically important CSI was rated as low. The certainty of evidence for the value of CCR was reduced by two, due to the risk of bias and heterogeneity in the included studies and increased by two, due to the very large magnitude of effect. Overall, the certainty of evidence for the value of CCR in detection of any CSI was rated as low. The certainty of evidence for the value of CCR in detection of clinically important CSI was lowered by one, due to the presence of publication bias and thus, was rated as very low (Table 4).

4. Discussion

Almost all suspected CSI patients undergo radiographic imaging due to the substantial impact of missing any clinically important CSI. The prevalence of CSI in suspected cervical trauma patients was shown to be roughly less than 4% in our included studies, therefore, many patients undergo unnecessary imaging. This causes a significant burden to patients and the healthcare system, such as prolonged ED administration duration, unnecessary radiation, and economic costs (30, 41).

Clinical decision rules (CDRs) have been recently developed to aid physicians in ruling out patients with a low risk of CSI. NEXUS and CCR are commonly known CDRs that have been shown to have acceptable performance indices in risk stratification of suspected CSI patients. The results of our study demonstrated an excellent AUC for CCR (>0.90), while NEXUS was shown to have a good AUC (>0.80). Our analysis showed that both NEXUS and CCR have excellent sensitivities (>0.90) in detecting CSIs, and CCR had a sensitivity of 1.00 with narrow CIs (compared to a sensitivity between 0.91 to 0.94 for NEXUS), which makes it a superior CDR for ruling out patients with a low risk of CSI. The similar results of the analysis on the studies with direct assessment of CCR and NEXUS add to the robustness of our findings.

The low specificity of the evaluated CDRs is expected in de-

cision rules designed for ruling out patients. Our analysis revealed a specificity of >0.30 for both NEXUS and CCR. Bearing in mind the significant number of suspected CSI patients presenting to the ED and the subsequent amount of radiographic imaging, even a small reduction in the number of requested imaging can have a sizeable impact on the overall radiographic imaging performed in the ED. It should also be mentioned that CCR had an extremely scarce number of false negatives compared to NEXUS and has a much lower chance of not detecting CSI.

While CCR performs better than NEXUS, NEXUS can be more readily implemented in clinical practice due to its constituents. CCR has more variables and requires information on the mechanism of injury, such as fall height and collision speed, which are not documented in most low and middle-income countries. Moreover, CCR requires examination of active neck rotation, and physicians occasionally omit this variable to avoid inflicting any injury to the cervical spine (24). Consequently, Ghelichkhani et al. (28) proposed a modified CCR excluding dangerous mechanisms and rear-end motor vehicle crashes. Their results demonstrated that the modified CCR had comparable performance to the original CCR with improved specificity. Further research could validate a modified CCR, making it more applicable in various clinical scenarios.

We also performed a subgroup analysis to evaluate the performance of NEXUS and CCR in geriatric and pediatric populations. According to CCR, all patients ≥ 65 years should undergo radiographic imaging, and for NEXUS, our analysis revealed a sensitivity of 0.97, with a wide CI (0.76 to 1.00) and an overall poor AUC. NEXUS was also shown to have poor performance in the pediatric population, and only three studies evaluated the performance of CCR in the pediatric population. Further studies are needed to investigate the value of NEXUS and CCR in geriatric and pediatric populations.

A recent systematic review and meta-analysis has investigated the performance of NEXUS and CCR in suspected CSI patients (13). In their review, Vazirizadeh-mahabadi and Yarahmadi included 5 studies with direct comparison of NEXUS and CCR and concluded that both CDRs have fair AUCs (0.70 and 0.79, respectively) with sensitivities of 0.89 (95% CI: 0.84 to 0.93) for NEXUS and 0.98 (95% CI: 0.95 to 0.99) for CCR. Our review provides more robust findings through the inclusion of more studies and addresses some limitations by providing analysis for all injuries, clinically important injuries, and pediatric and geriatric patients.

5. Limitations

Our review has its limitations. Few included studies had utilized a modified version of the decision rules, which could introduce bias in the results. Moreover, studies had not reported the injury severity scores of their patient populations, and few studies had included patients with GCS < 15. Considering that CCR was initially designed to be utilized in stable and alert patients, the application of CCR in patients with GCS < 15 is not in line with its original purpose. However, patients with an altered state of consciousness are more likely to be ruled in for more evaluations, and the true difficulty lies in decision-making for awake and alert patients with minimal to no physical findings (8), and thus we believe this limitation had a negligible impact on the validity of the results of our study. It should also be mentioned that the prespecified low level of evidence in GRADE for observational studies could cause a misjudgment in the assessment of the level of evidence, and according to the Centre for Evidence-Based Medicine (CEBM) recommendations, systematic reviews of observational studies are among the studies with the highest levels of evidence (50).

6. Conclusion

Our study demonstrates that both NEXUS and CCR can be used in ruling out patients with low risk of CSI, and CCR was shown to have superior performance. Even though these tools have low specificity, their application can still greatly reduce the number of radiographic imaging performed in emergency departments.

7. Declarations

7.1. Acknowledgments

None.

7.2. Conflict of interest

The authors declare that they have no conflicting interests.

7.3. Funding

None.

7.4. Authors' contribution

Study design: AB; Data gathering: AB, KA; Analysis: MY, KA; Interpretation of results: all authors; Drafting and revising: all authors

7.5. Availability of data and materials

The gathered data and checklist can be provided to qualified researchers with the intent of replicating the procedure and results.

7.6. Using artificial intelligence chatbots

None.

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Table 1: Characteristics of the included studies

Study, Year	Design*	Sample size	Age (year)	Patient group	Male %	Outcome	Index test	N CSI	N normal
Ala, 2018 [19]	Prospective	200	40.00 ± 17.75	Adult	69.5	All CSI	NEXUS, CCR	10	190
Benayoun, 2018 [7]	Retrospective	689 533	53.6	Adult	63.5	All CSI	NEXUS CCR	7 7	682 526
Chamberlin, 2020 [20]	Retrospective	405	NR	All patients	NR	All CSI	NEXUS	10	395
Chaudry, 2012 [21]	Retrospective	641	37.7 ± 12.5	Adult	85.5	All CSI	NEXUS	7	634
Coffey, 2011 [48]	Prospective	1420	NR	Adult	50.4	All CSI	CCR	8	1412
Dahlquist, 2015 [22]	Retrospective	566	34	All patients	65.3	Important# CSI	NEXUS	53	513
Denver, 2015 [23]	Prospective	169	80.2 ± 8.3	Geriatric	30.2	All CSI Important CSI	NEXUS	11 9	158 160
Dickinson, 2004 [24]	Prospective	8924	36.7 ± 16	Adult	51.5	All CSI Important CSI	NEXUS	179 151	8745 8773
Duane, 2012 [25]	Prospective	5182	38.76	Adult	NR	All CSI	NEXUS, CCR	324	4858
Ehrlich, 2009 [26]	Retrospective	108 109	4.3 ± 3.1	Pediatric	57.6	Important CSI	NEXUS CCR	7 7	101 102
Engelbart, 2022 [27]	Retrospective	2312	81.02	Geriatric	39.1	All CSI	NEXUS	253	2059
Evans, 2015 [28]	Retrospective	643	81	Geriatric	48.5	All CSI	NEXUS	50	593
Ghelichkhani, 2020 [29]	Prospective	673	34.3 ± 19.4	Adult	69.24	Important CSI	NEXUS, CCR	61	612
Goode, 2014 [30]	Prospective	320	74.69 ± 7.73	Geriatric	54.4	All CSI	NEXUS	41	279
Griffith, 2011 [31]	Retrospective	1565	43.4	Adult	58.8	All CSI	NEXUS	41	1524
Griffith, 2013 [32]	Prospective	502 411	44	Adult	61.5	All CSI	NEXUS CCR	5 4	497 407
Griffith, 2014 [33]	Prospective	382 314	47.7	Adult	56.8	All CSI	NEXUS CCR	12 8	370 306
Hoffman, 2000 [8]	Prospective	34069	37	All patients	58.7	All CSI Important CSI	NEXUS	818 578	33251 33491
Jaffe, 1987 [50]	Retrospective	206	NR	Pediatric	69.4	All CSI	NEXUS	59	147
Jambhekar, 2018 [34]	Prospective	596	81.1 ± 8.8	Geriatric	NR	All CSI	NEXUS	10	586
Kavak, 2018 [35]	Retrospective	1317	41.2 ± 18.8	Adult	63.9	Important CSI	NEXUS	14	1303
Migliore, 2011 [49]	Prospective	61	NR	All patients	NR	All CSI	NEXUS	1	60
Miller, 2006 [36]	Prospective	444	34.2	Adult	50.2	Important CSI	CCR	3	441
Moak, 2011 [37]	Prospective	124	NR	Adult	NR	Important CSI	NEXUS	29	95
Pepin, 2015 [38]	Retrospective	405 318	14	Pediatric	66.6	All CSI	NEXUS CCR	4 4	401 314
Phillips, 2021 [39]	Prospective	973	10.9	Pediatric	66.1	Important CSI	NEXUS, CCR	5	968
Puttum, 2014 [40]	Prospective	1008	37.7 ± 12.5	All patients	88.5	All CSI	NEXUS, CCR	361	647
Rethnam, 2008 [41]	Retrospective	114	NR	Adult	53.2	Important CSI	CCR	2	112
Stiell, 2001 [9]	Prospective	8924	36.7 ± 16	Adult	51.5	Important CSI	CCR	151	8773
Stiell, 2003 [42]	Prospective	7438	37.6 ± 16	Adult	58.2	Important CSI	NEXUS, CCR	162	7276
Stiell, 2010 [43]	Prospective	3452	41 ± 18	Adult	48.9	Important CSI	CCR	41	3411
Touger, 2002 [44]	Prospective	33386	37	Adult	58	All CSI	NEXUS	818	32568
Tran, 2016 [45]	Prospective	799	85	Geriatric	33.2	Important CSI	NEXUS	11	788
Vaillancourt, 2009 [46]	Prospective	1629	39	Adult	58.9	Important CSI	CCR	12	1617
Viccellio, 2001 [47]	Prospective	3065	12.36	Pediatric	NR	All CSI	NEXUS	30	3035

* All studies were designed as observational studies. #: Clinically important CCR: Canadian C-spine Rule;
CSI: Cervical Spinal Injury; NEXUS: National Emergency X-Radiography Utilization Study; NR: Not Reported.

Table 2: Performance values of NEXUS and CCR in detection of CSI

Decision Rule	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PLR (95% CI)	NLR (95% CI)	DOR (95% CI)
Any CSI						
NEXUS	0.85 (0.81 to 0.87)	0.94 (0.91 to 0.97)	0.32 (0.22 to 0.44)	1.4 (1.2 to 1.6)	0.17 (0.10 to 0.29)	7.96 (4.35 to 14.58)
CCR	0.97 (0.96 to 0.98)	1.00 (0.98 to 1.00)	0.34 (0.20 to 0.51)	1.5 (1.2 to 1.9)	0.01 (0.00 to 0.05)	185 (27 to 1252)
Clinically important CSI						
NEXUS	0.78 (0.74 to 0.81)	0.95 (0.89 to 0.98)	0.41 (0.31 to 0.52)	1.6 (1.4 to 1.9)	0.13 (0.07 to 0.25)	12.25 (6.21 to 24.16)
CCR	0.94 (0.91 to 0.96)	1.00 (0.95 to 1.00)	0.37 (0.25 to 0.52)	1.6 (1.3 to 2.0)	0.01 (0.00 to 0.14)	235.59 (10.67 to 5201.97)
Direct assessment (any CSI)						
NEXUS	0.80 (0.76 to 0.83)	0.91 (0.86 to 0.95)	0.36 (0.28 to 0.46)	1.4 (1.3 to 1.6)	0.24 (0.15 to 0.38)	5.98 (3.49 to 10.23)
CCR	0.96 (0.94 to 0.98)	1.00 (0.98 to 1.00)	0.27 (0.13 to 0.48)	1.4 (1.1 to 1.8)	0.01 (0.00 to 0.08)	123.42 (16.22 to 939.37)

AUC: Area Under the Curve; CCR: Canadian C-spine Rule; CSI: Cervical Spinal Injury; DOR: Diagnostic Odds Ratio; CI: confidence interval NEXUS: National Emergency X-Radiography Utilization Study; NLR: Negative Likelihood Ratio; PLR: Positive Likelihood Ratio.

Table 3: Quality assessment of the included studies

Study, year	Risk of Bias				Applicability			Overall
Ala, 2018 [19]	Low	Low	Low	Low	Low	Low	Low	Low
Benayoun, 2016 [7]	Low	Unclear	Low	Low	Low	Low	Low	Some concern
Chamberlin, 2020 [20]	Unclear	Unclear	Unclear	Low	Low	Low	Low	Some concern
Chaudry, 2012 [21]	Unclear	Unclear	Unclear	Low	Low	Low	Low	Some concern
Coffey, 2011 [48]	Unclear	Low	Unclear	Low	Low	Low	Low	Some concern
Dahlquist, 2015 [22]	Low	Unclear	Unclear	Low	Low	Low	Low	Some concern
Denver, 2015 [23]	Low	Low	Unclear	Low	Low	Low	Low	Some concern
Dickinson, 2004 [24]	Unclear	Low	Low	Low	Low	Low	Low	Some concern
Duane, 2012 [25]	Unclear	Low	Unclear	Low	Low	High	Low	Some concern
Ehrlich, 2009 [26]	Low	Low	Low	Low	Low	Low	Low	Some concern
Engelbart, 2022 [27]	Low	High	High	Low	Low	Low	Low	Some concern
Evans, 2015 [28]	Low	Unclear	Unclear	Low	Low	Low	Low	Some concern
Ghelichkhani, 2021 [29]	High	Low	Low	Low	Low	Low	Low	Some concern
Goode, 2014 [30]	Unclear	Unclear	Unclear	Low	Low	Low	Low	Some concern
Griffith, 2011 [31]	Low	Unclear	Low	Low	Low	Low	Low	Some concern
Griffith, 2013 [32]	High	Low	Low	Low	Low	High	Low	Some concern
Griffith, 2014 [33]	High	Unclear	Low	Low	Low	High	Low	Some concern
Hoffman, 2000 [8]	Low	Low	Low	Low	Low	Low	Low	Low
Jaffe, 1987 [50]	Low	Unclear	Unclear	Low	Low	High	Low	Some concern
Jambhekar,2018 [34]	High	Low	Unclear	Low	Low	Low	Low	Some concern
Kavak, 2018 [35]	Low	Unclear	Unclear	Low	Low	Low	Low	Some concern
Migliore, 2011 [49]	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Some concern
Miller, 2006 [36]	Unclear	Low	High	Low	Low	Low	Low	Some concern
Moak, 2011 [37]	High	Low	Unclear	Unclear	Low	Low	Low	Some concern
Pepin, 2015 [38]	Low	Low	Unclear	Unclear	Low	Low	Low	Some concern
Phillips, 2021 [39]	Low	Low	Unclear	Low	Low	Low	Low	Some concern
Puttum, 2014 [40]	Unclear	Low	Unclear	Low	Low	Low	Low	Some concern
Rethnam, 2008 [41]	Low	Unclear	Unclear	Low	Low	Low	Low	Some concern
Stiell, 2001 [9]	Unclear	Low	Low	Low	Low	Low	Low	Some concern
Stiell, 2003 [42]	Low	Low	Low	Low	Low	Low	Low	Low
Stiell, 2010 [43]	High	Low	Low	Low	Low	Low	Low	Some concern
Touger, 2002 [44]	Low	Low	Low	Low	Low	Low	Low	Low
Tran, 2016 [45]	High	Low	Unclear	Low	Low	High	Low	Some concern
Vaillancourt, 2009 [46]	High	Low	Low	Low	Low	High	Low	Some concern
Viccellio, 2001 [47]	Low	Low	Low	Low	Low	Low	Low	Some concern

Table 4: Certainty of Evidence

Index test	N studies, N patients, Event rate	Risk of bias	Heterogeneity	Indirectness	Imprecision	Publication bias	Other considerations
All CSI							
NEXUS	26 69957 3.5%	Serious	Serious	Not present	Not present	Not present	Very large magnitude of effect
CCR	17 33142 3.5%	Serious	Serious	Not present	Not present	Not present	Very large magnitude of effect
Clinically important CSI							
NEXUS	12 55565 1.9%	Serious	Serious	Not present	Not present	Not present	Very large magnitude of effect
CCR	10 24074 1.8%	Serious	Serious	Not present	Not present	Present	Very large magnitude of effect

CCR: Canadian C-spine Rule; CSI: Cervical Spinal Injury; NEXUS: National Emergency X-Radiography Utilization Study.

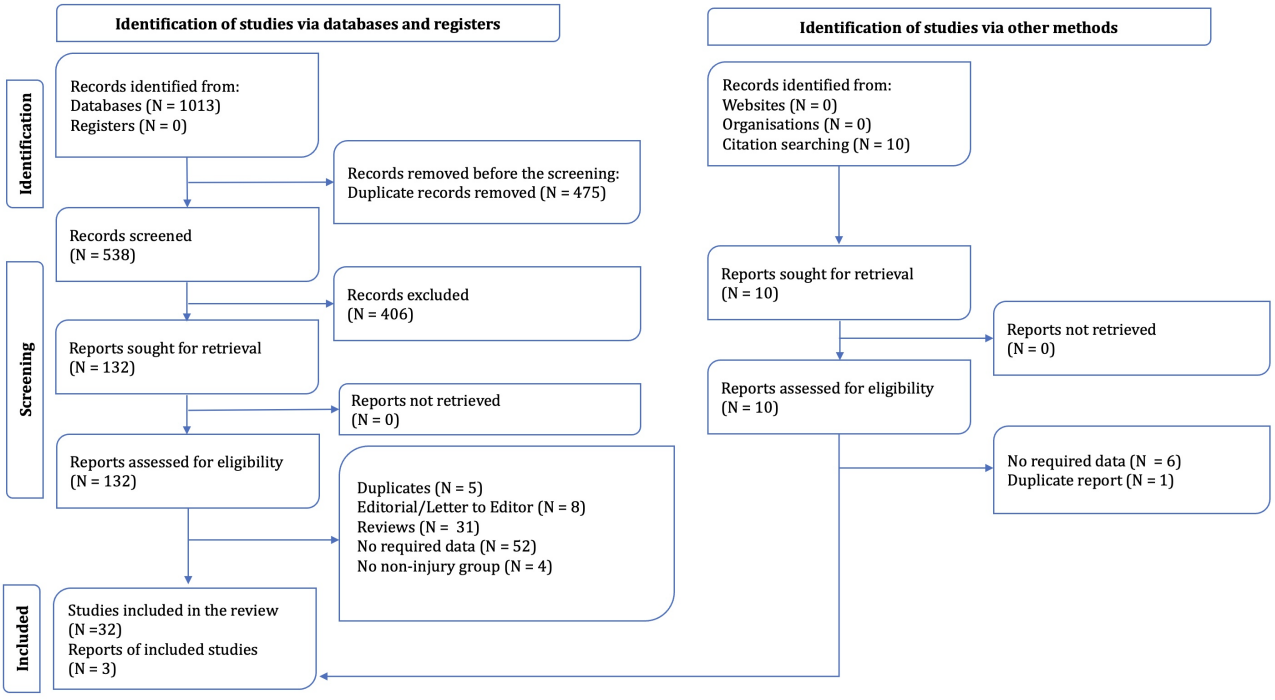

Figure 1: Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram of the included studies.

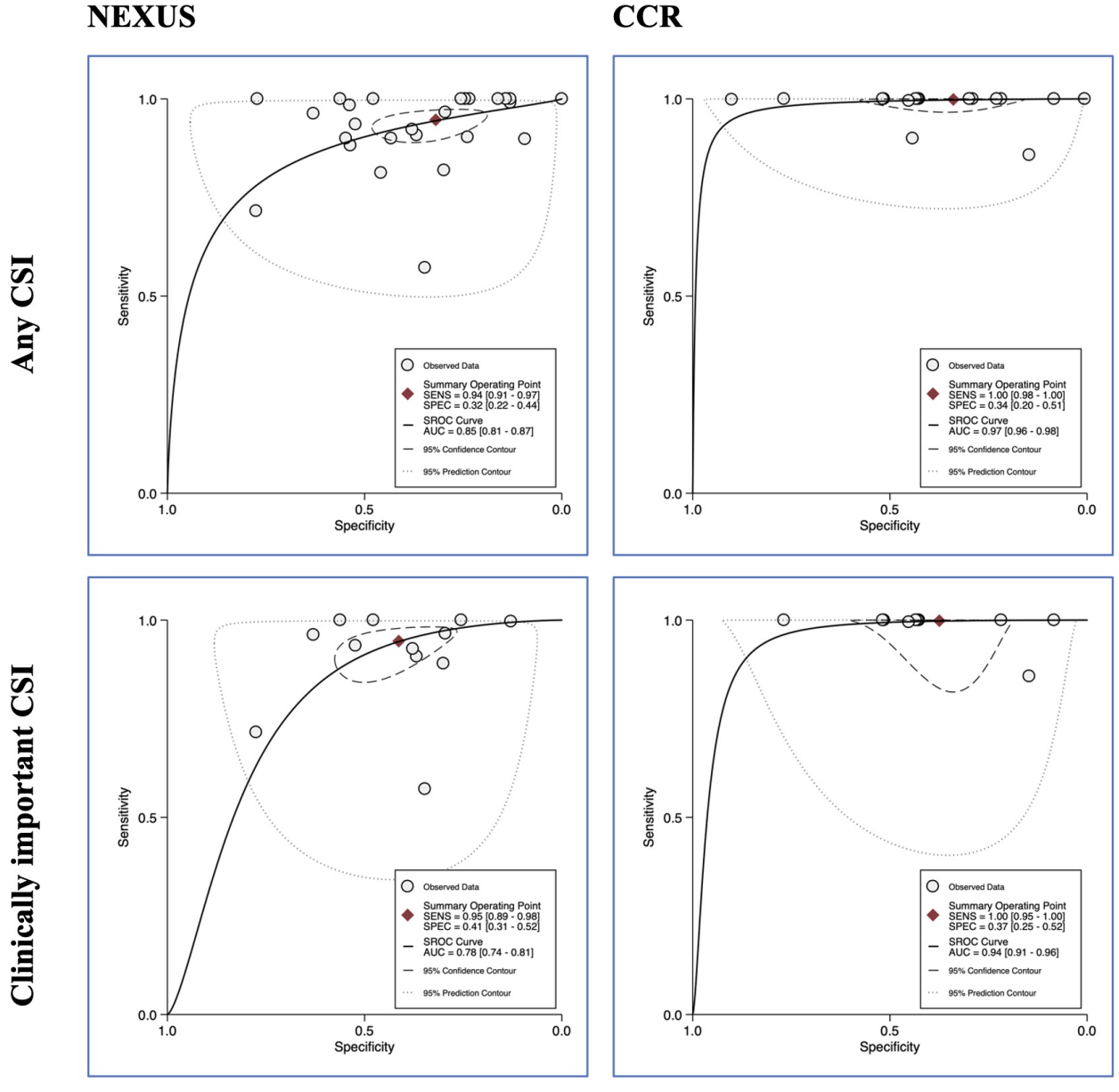

Figure 2: The area under the receiver operating characteristic curve of NEXUS and CCR in detection of any cervical spine injury (CSI) and clinically important CSI.

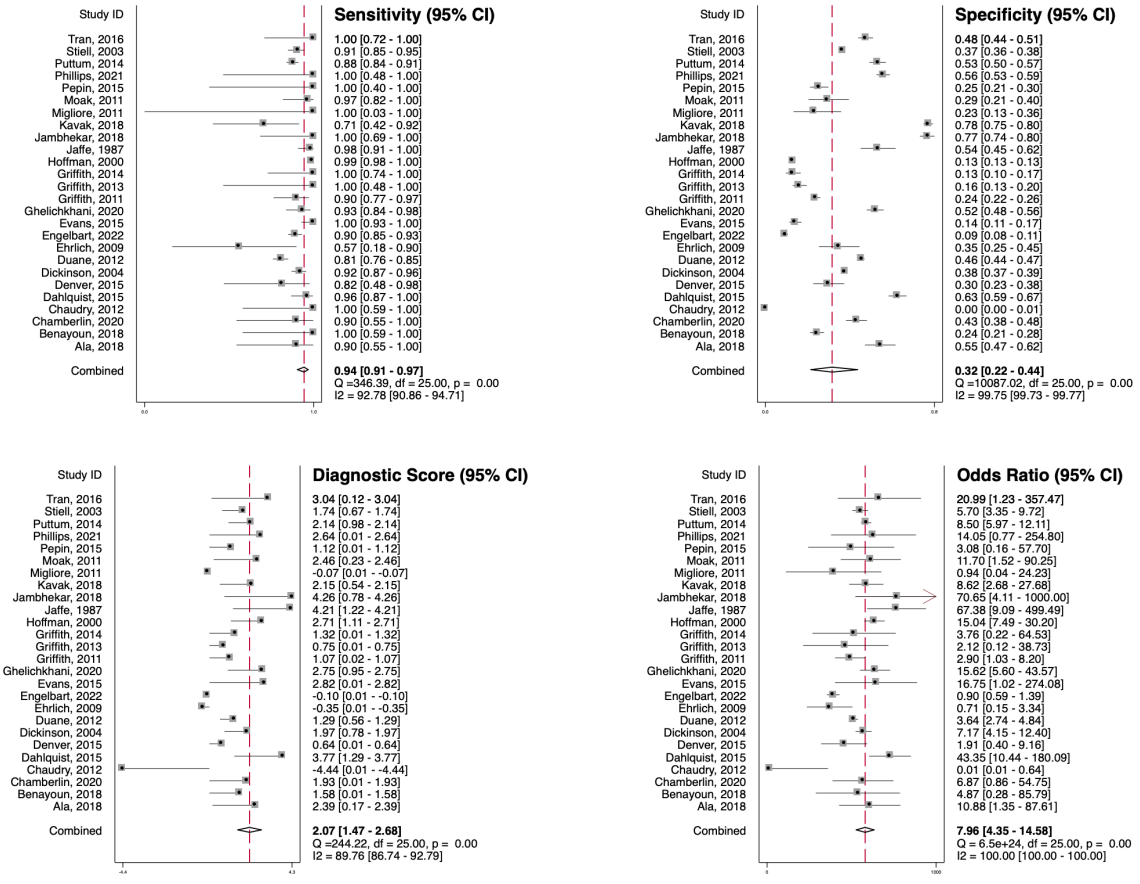

Figure 3: Sensitivity, specificity, and diagnostic odds ratio of NEXUS in detection of any cervical spine injury. CI: confidence interval.

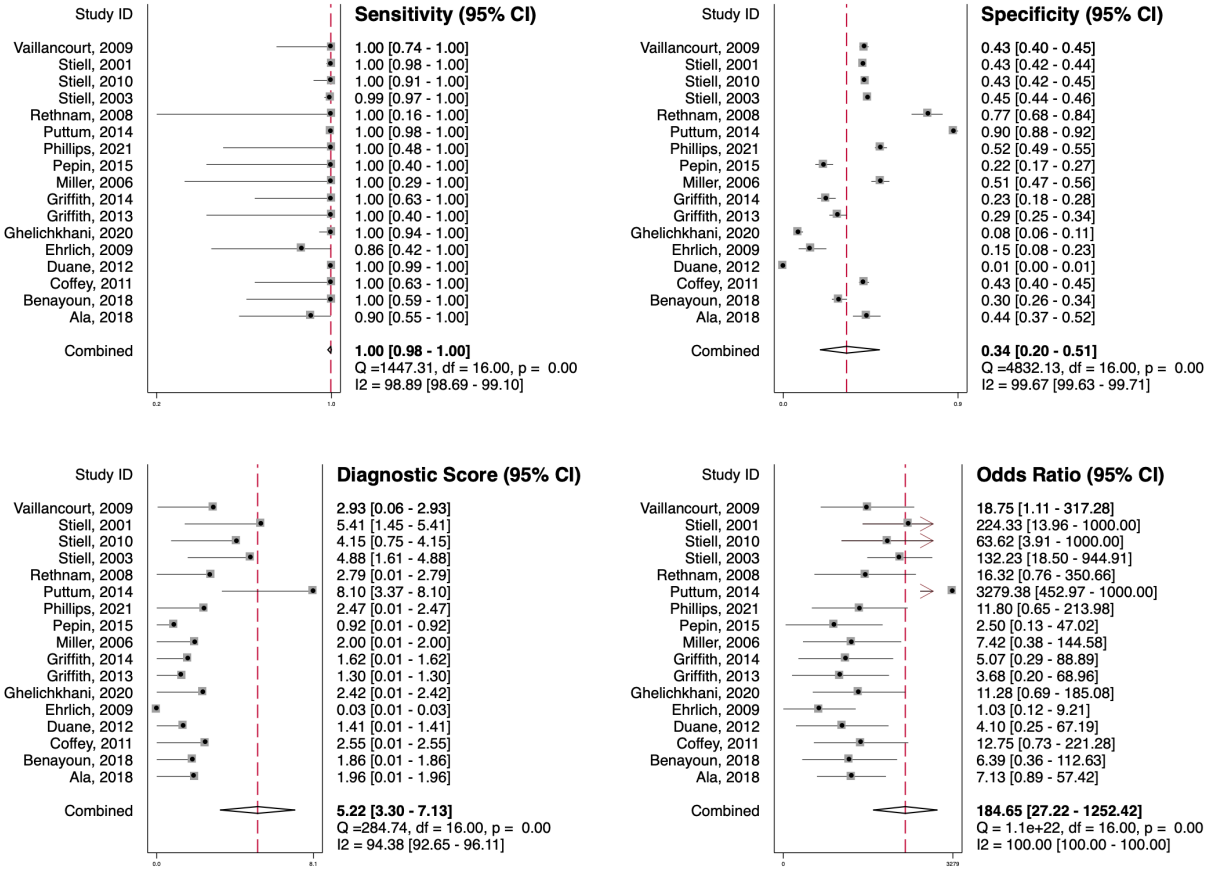

Figure 4: Sensitivity, specificity, and diagnostic odds ratio of CCR in detection of any cervical spine injury. CI: confidence interval.

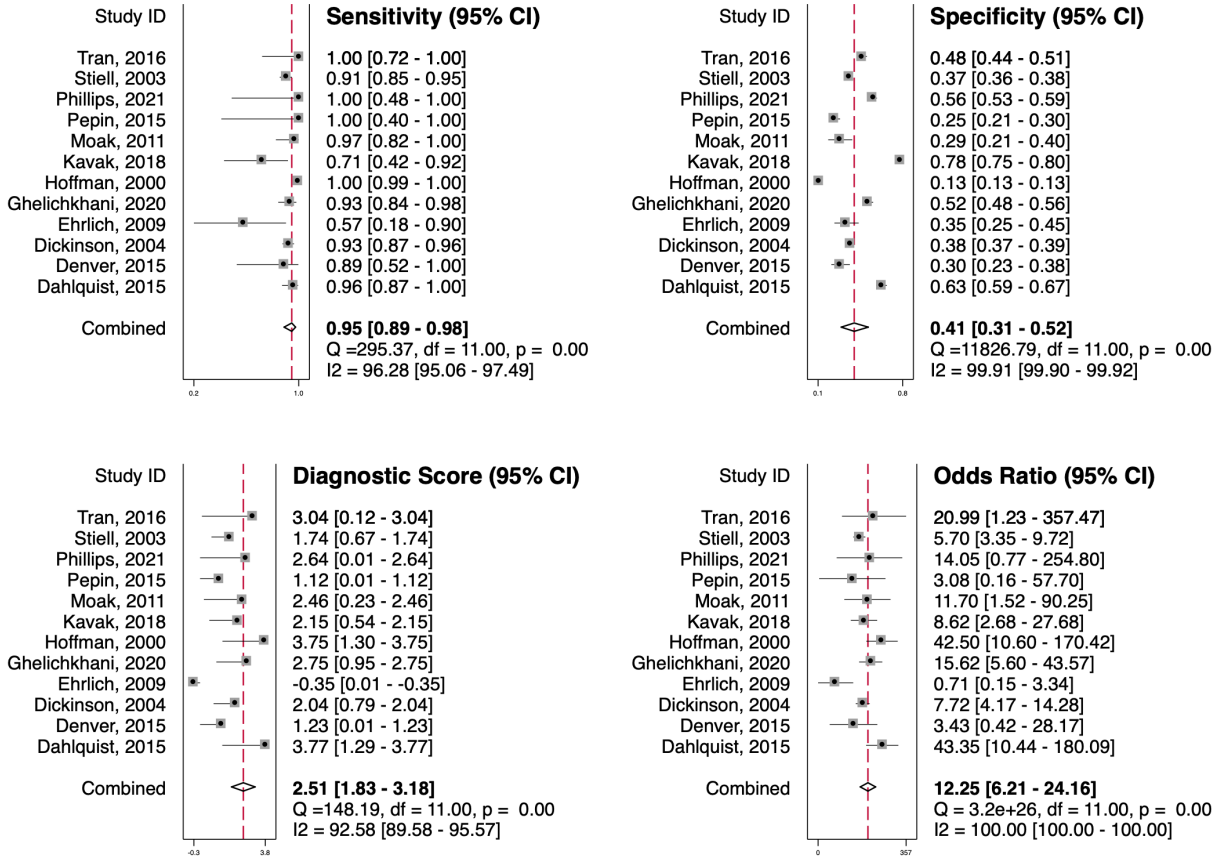

Figure 5: Sensitivity, specificity, and diagnostic odds ratio of NEXUS in detection of clinically important cervical spine injury. CI: confidence interval.

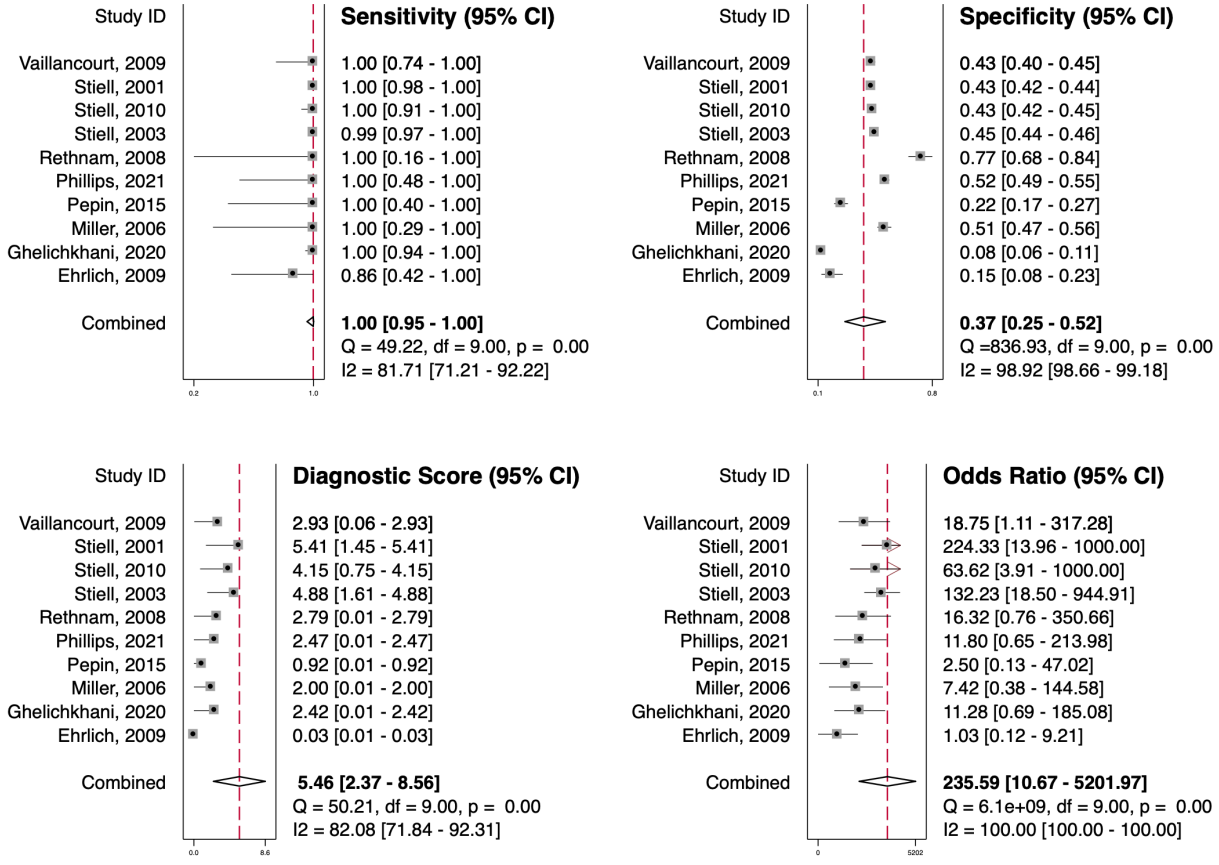

Figure 6: Sensitivity, specificity, and diagnostic odds ratio of CCR in detection of clinically important cervical spine injury. CI: confidence interval.

Supplementary table 1: The study search strategy in different databases

PubMed:
"Clinical decision rules"[mh] OR "Decision Support Techniques"[mh] OR Clinical decision rule[tiab] OR Clinical prediction rule[tiab] OR Decision support technique[tiab] OR decision support technic[tiab] OR Decision support model[tiab] OR decision modeling[tiab] OR decision aid[tiab] OR decision analysis[tiab] OR decision analyses[tiab] OR Canadian C-Spine[tiab] OR Canadian c-spine rule[tiab] OR Canadian c spine[tiab] OR Canadian c spine rule[tiab] OR National Emergency X-Radiography Utilization Study[tiab] OR NEXUS[tiab] OR low risk spine criteria[tiab] OR Decision model[tiab] OR decision analysis[tiab] OR decision analysis model[tiab] OR clinical decisions rules[tiab] OR clinical predictions rules[tiab] OR Decision suppor*[tiab] OR CDS system[tiab] OR clinical decision support system[tiab] OR Appropriateness Criteria[tiab] OR decision too*[tiab] AND "Neck injuries"[mh] OR "Whiplash Injuries"[mh] OR Neck injury[tiab] OR Whiplash injury[tiab] OR Cervical spinal cord injury[tiab] OR cervical spine injury[tiab] OR cervical spine fracture[tiab] OR neck bruise[tiab] OR neck injuries[tiab] OR neck lesion[tiab] OR trauma colli[tiab] OR cervical cord injury[tiab] OR cervical cord lesion[tiab] OR cervical spinal cord lesion[tiab] OR cervical spinal cord injury[tiab] OR cervical spinal cord trauma[tiab] OR cervical spine cord lesion[tiab] OR cervical spinal injury[tiab] OR cervical spinal trauma[tiab] OR cervical spine trauma[tiab] OR cervical trauma[tiab] OR broken neck[tiab] OR cervical fracture[tiab] OR cervical spinal fracture[tiab] OR cervical spine fracture[tiab] OR cervical vertebra fracture[tiab] OR cervical vertebral fracture[tiab] OR fractured cervical spine[tiab] OR fractured cervical vertebra[tiab] OR fractured cervical vertebrae[tiab] OR neck fracture[tiab]
Embase:
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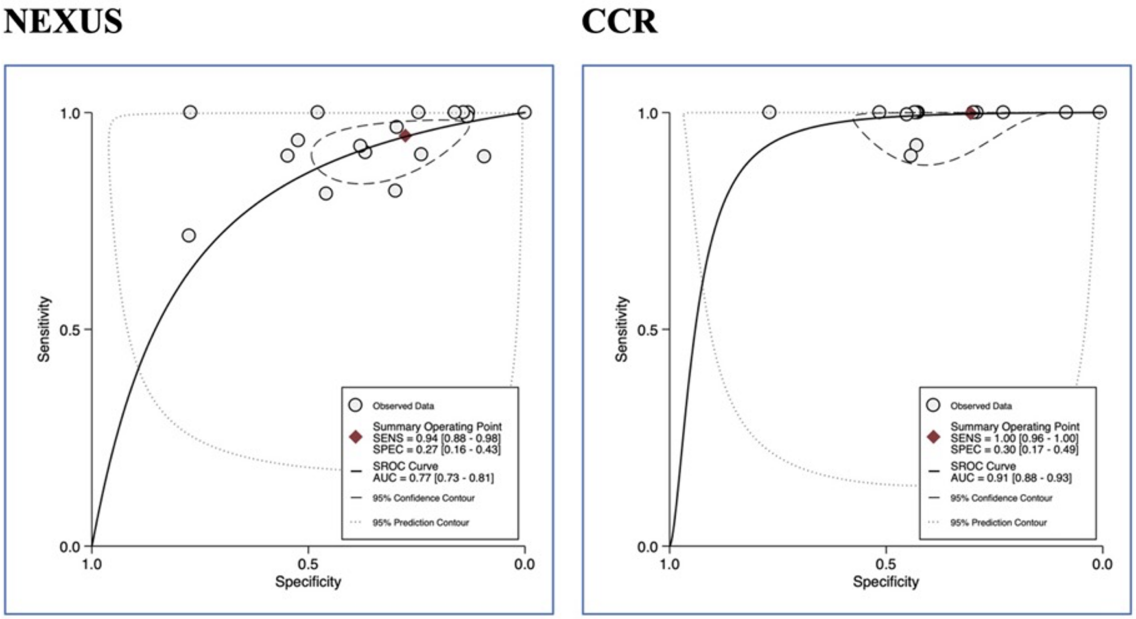
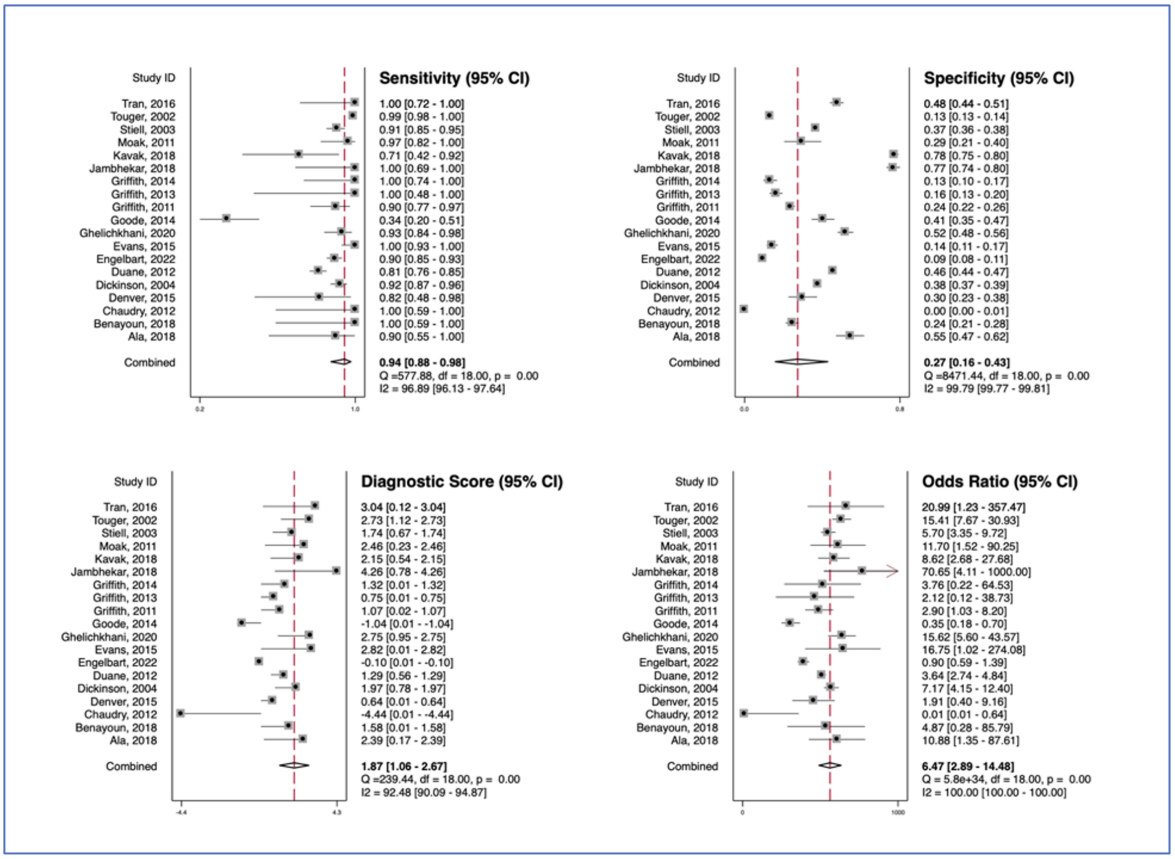
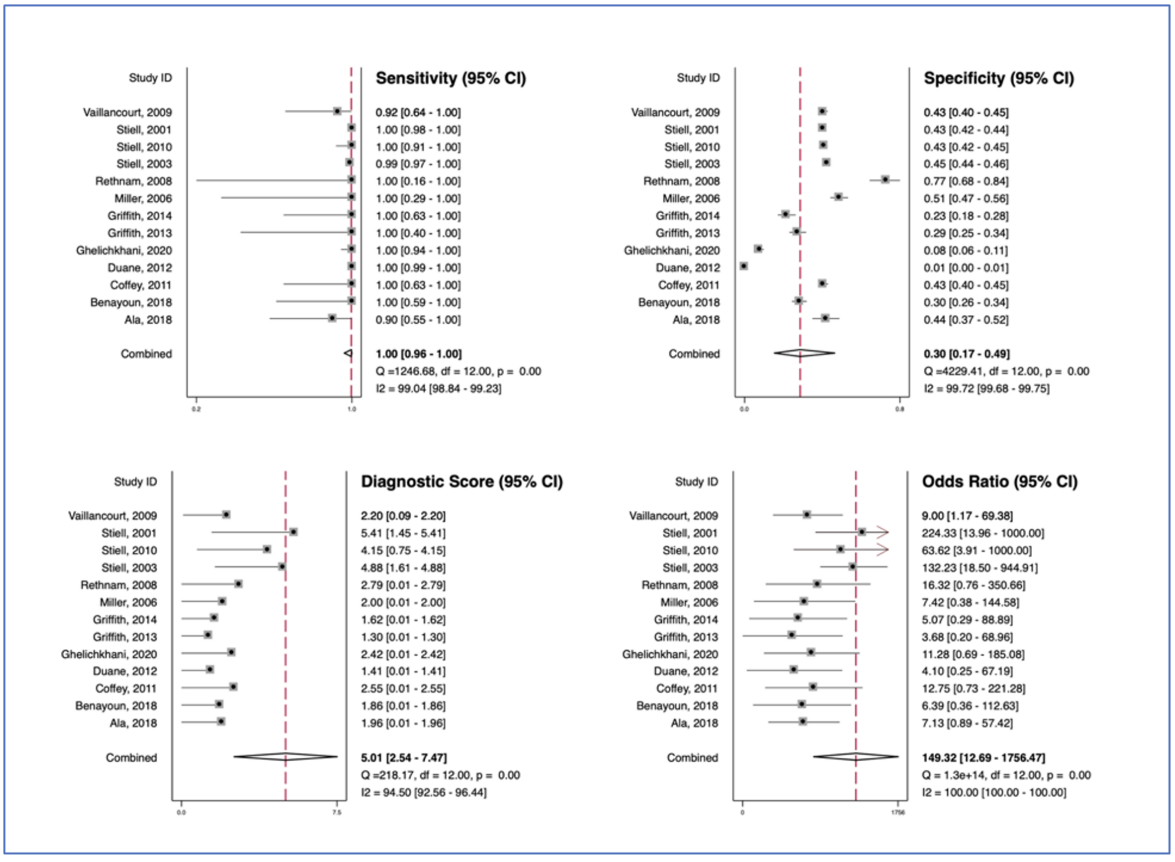
Web of Science:
TS=("clinical decision rule" OR "decision support system" OR "clinical decision support system" OR "Appropriateness Criteria" OR "decision model" OR "decision analysis" OR "decision analysis model" OR "clinical decision rules" OR "clinical decisions rules" OR "clinical prediction rule" OR "clinical predictions rules" OR "decision support" OR "CDS system" OR "decision support technique" OR "decision support technic" OR "decision support model" OR "Decision aid" OR "decision analysis" OR "decision analyses" OR "Canadian C-spine" OR "Canadian C spine" OR "Canadian c-spine rule" OR "canadian c spine rule" OR "National emergency X-radiography utilization study" OR "NEXUS" OR "Low risk spine criteria" OR "decision tool" OR "decision tools") AND TS=("neck injury" OR "cervical spinal cord injury" OR "cervical spine injury" OR "cervical spine fracture" OR "neck bruise" OR "neck injuries" OR "neck lesion" OR "trauma colli" OR "cervical cord injury" OR "cervical cord lesion" OR "cervical spinal cord lesion" OR "cervical spinal cord injury" OR "cervical spinal cord trauma" OR "cervical spine cord lesion" OR "cervical spinal injury" OR "cervical spinal trauma" OR "cervical spine trauma" OR "cervical trauma" OR "broken neck" OR "cervical fracture" OR "cervical spinal fracture" OR "cervical spine fracture" OR "cervical vertebra fracture" OR "cervical vertebral fracture" OR "fractured cervical spine" OR "fractured cervical vertebra" OR "fractured cervical vertebrae" OR "neck fracture" OR "Whiplash injury" OR "Whiplash injuries")
Scopus:
TITLE-ABS-KEY("clinical decision rule" OR "decision support system" OR "clinical decision support system" OR "Appropriateness Criteria" OR "decision model" OR "decision analysis" OR "decision analysis model" OR "clinical decision rules" OR "clinical decisions rules" OR "clinical prediction rule" OR "clinical predictions rules" OR "decision support" OR "CDS system" OR "decision support technique" OR "decision support technic" OR "decision support model" OR "Decision aid" OR "decision analysis" OR "decision analyses" OR "Canadian C-spine" OR "Canadian C spine" OR "Canadian c-spine rule" OR "canadian c spine rule" OR "National emergency X-radiography utilization study" OR "NEXUS" OR "Low risk spine criteria" OR "decision tool" OR "decision tools") AND TITLE-ABS-KEY("neck injury" OR "cervical spinal cord injury" OR "cervical spine injury" OR "cervical spine fracture" OR "neck bruise" OR "neck injuries" OR "neck lesion" OR "trauma colli" OR "cervical cord injury" OR "cervical cord lesion" OR "cervical spinal cord lesion" OR "cervical spinal cord injury" OR "cervical spinal cord trauma" OR "cervical spine cord lesion" OR "cervical spinal injury" OR "cervical spinal trauma" OR "cervical spine trauma" OR "cervical trauma" OR "broken neck" OR "cervical fracture" OR "cervical spinal fracture" OR "cervical spine fracture" OR "cervical vertebra fracture" OR "cervical vertebral fracture" OR "fractured cervical spine" OR "fractured cervical vertebra" OR "fractured cervical vertebrae" OR "neck fracture" OR "Whiplash injury" OR "Whiplash injuries")



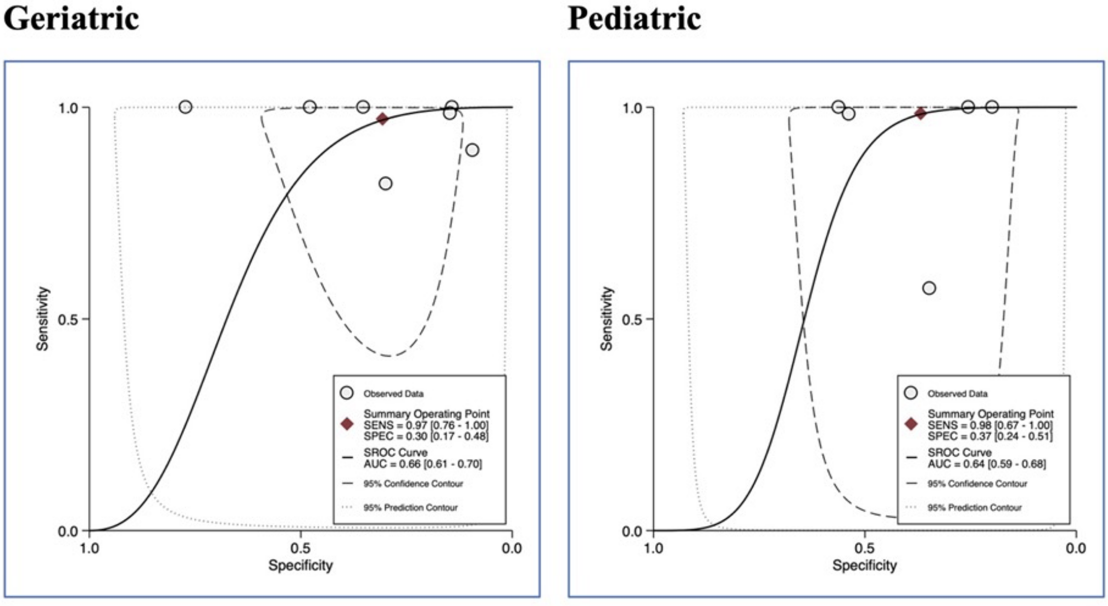
Supplementary Figure 1: Area under the receiver operating characteristic curve of NEXUS and CCR in detection of any cervical spine injury (CSI) in adult patients.



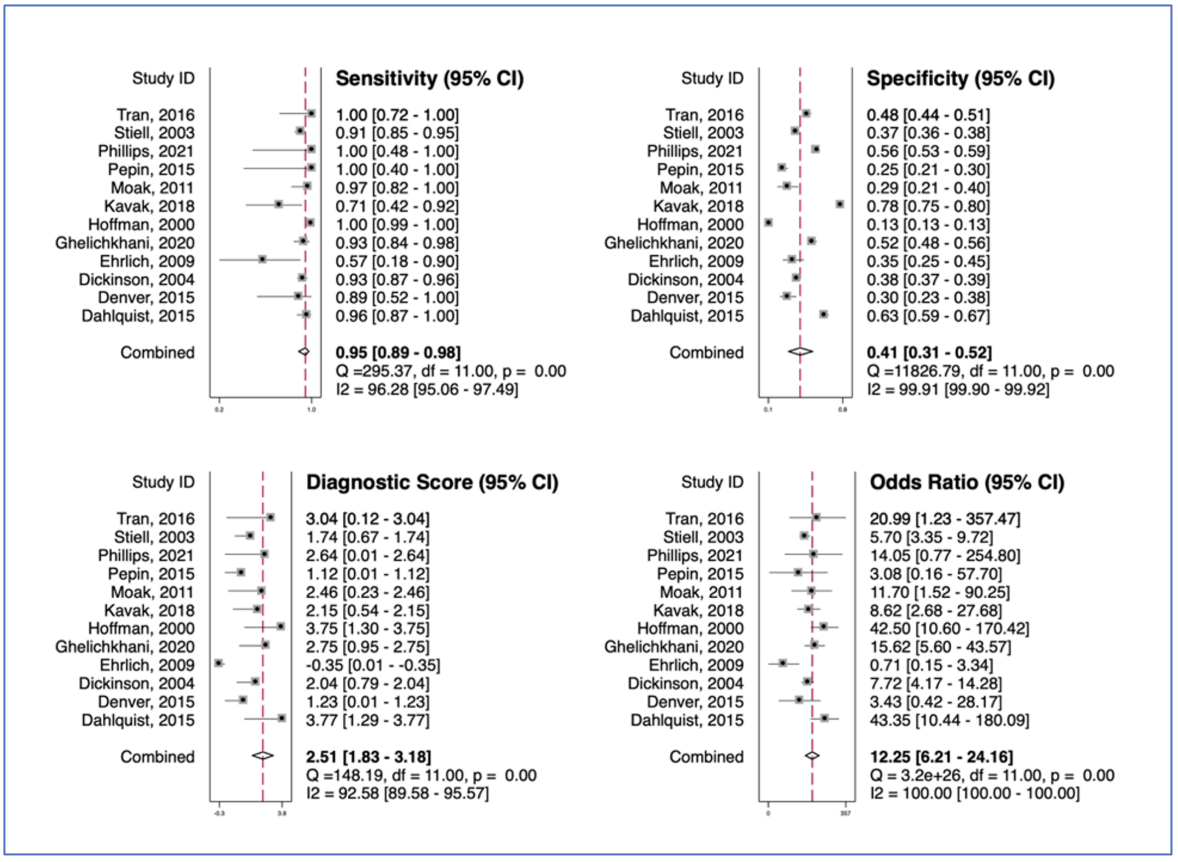
Supplementary Figure 2: Sensitivity, specificity, and diagnostic odds ratio of NEXUS in detection of any cervical spine injury in adult patients. CI: confidence interval.



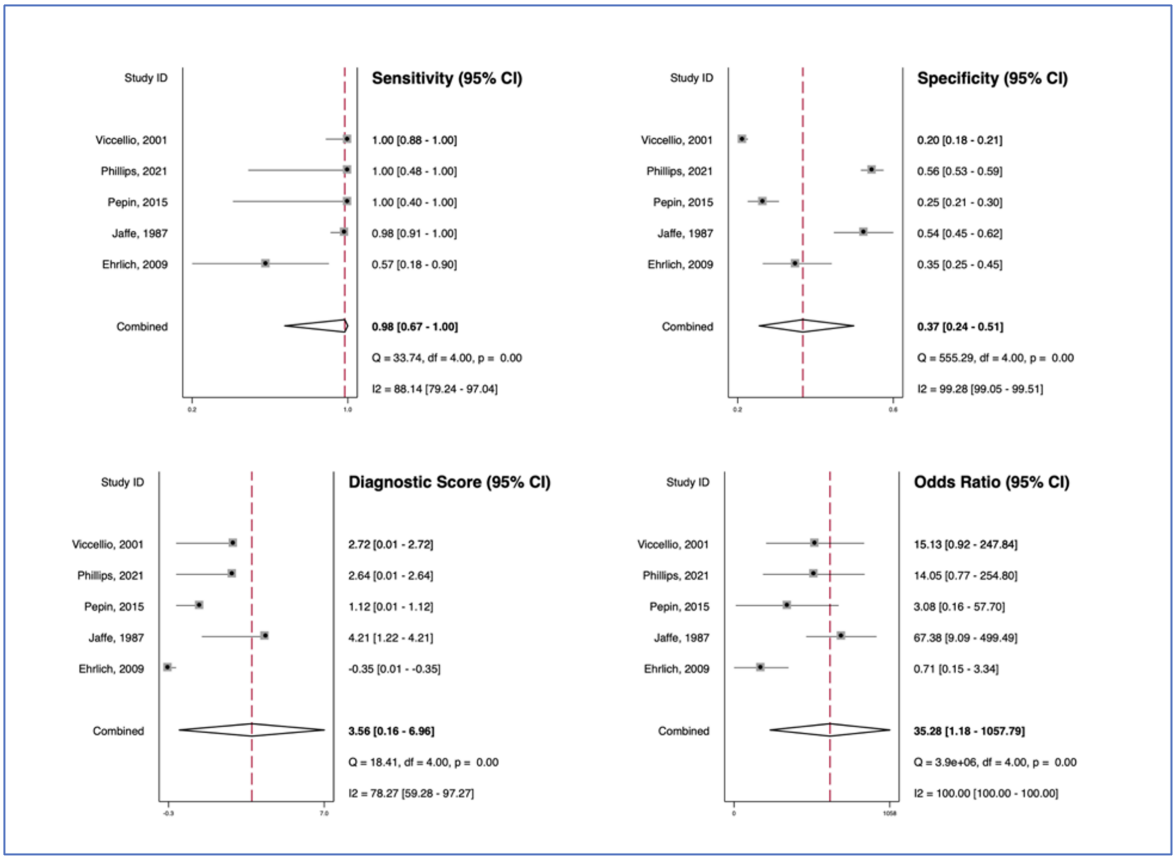
Supplementary Figure 3: Sensitivity, specificity, and diagnostic odds ratio of CCR in detection of any cervical spine injury in adult patients. CI: confidence interval.



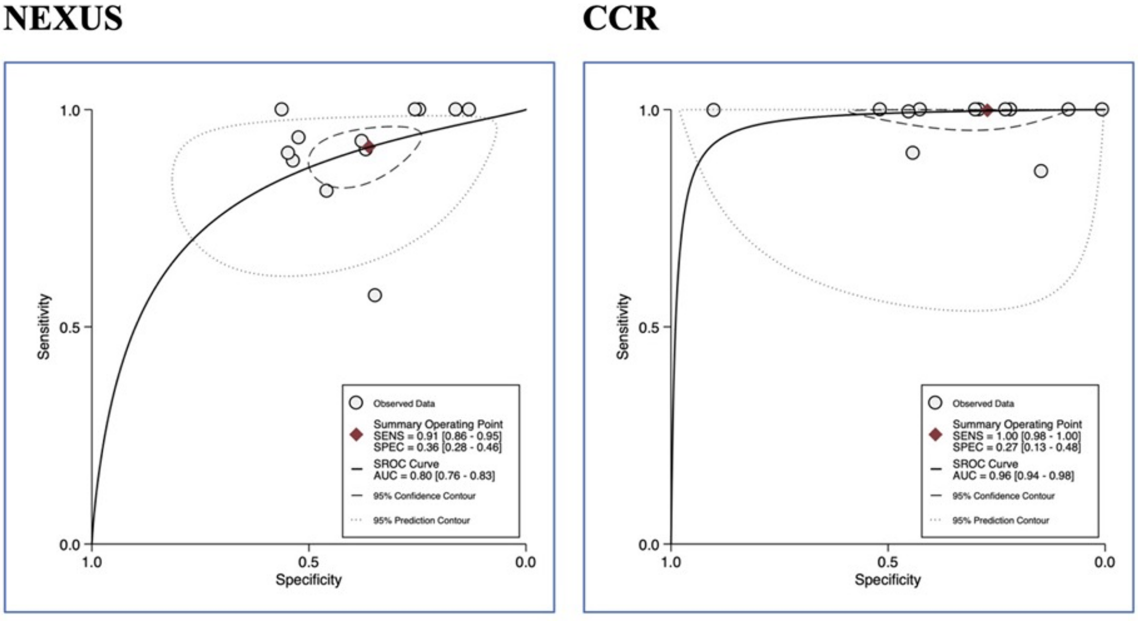
Supplementary Figure 4: Area under the receiver operating characteristic curve of NEXUS in detection of any cervical spine injury in geriatric and pediatric patients.



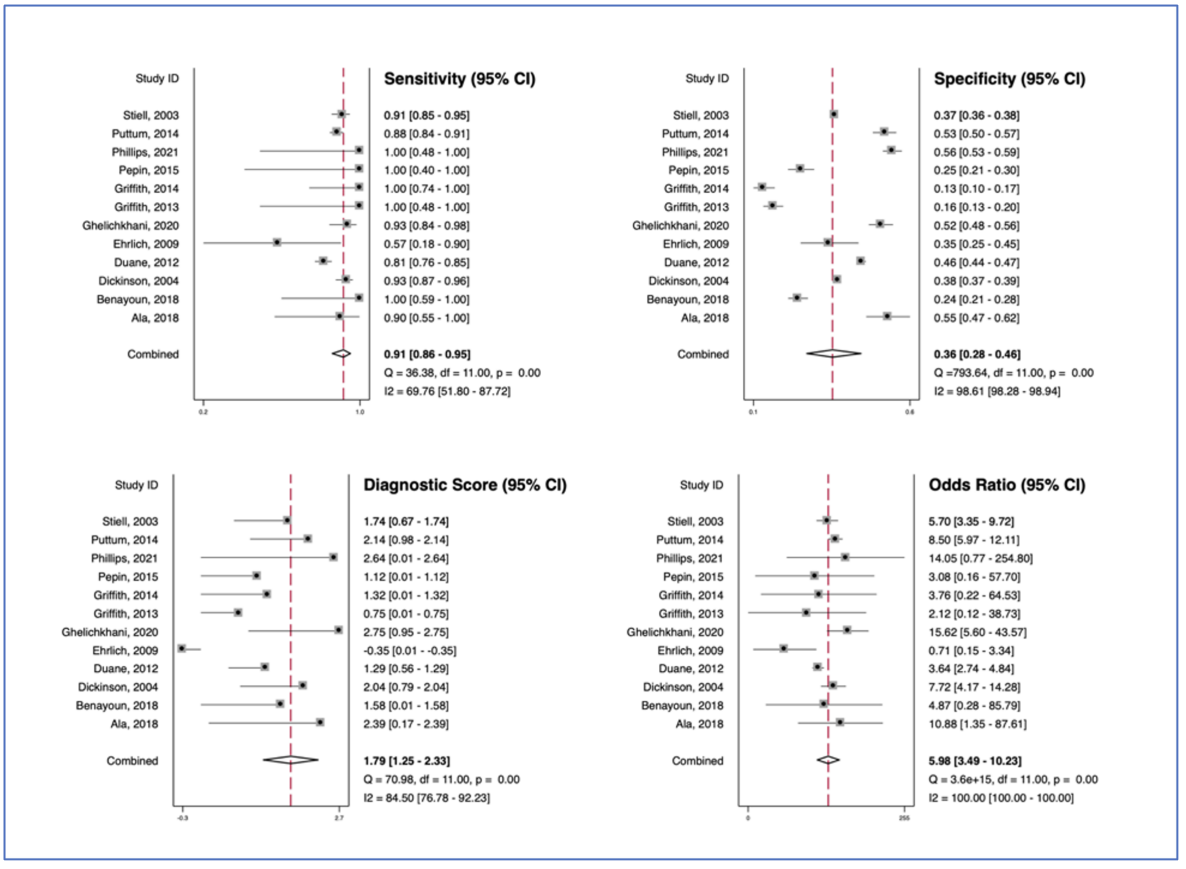
Supplementary Figure 5: Sensitivity, specificity, and diagnostic odds ratio of NEXUS in detection of any cervical spine injury in geriatric patients. CI: confidence interval.



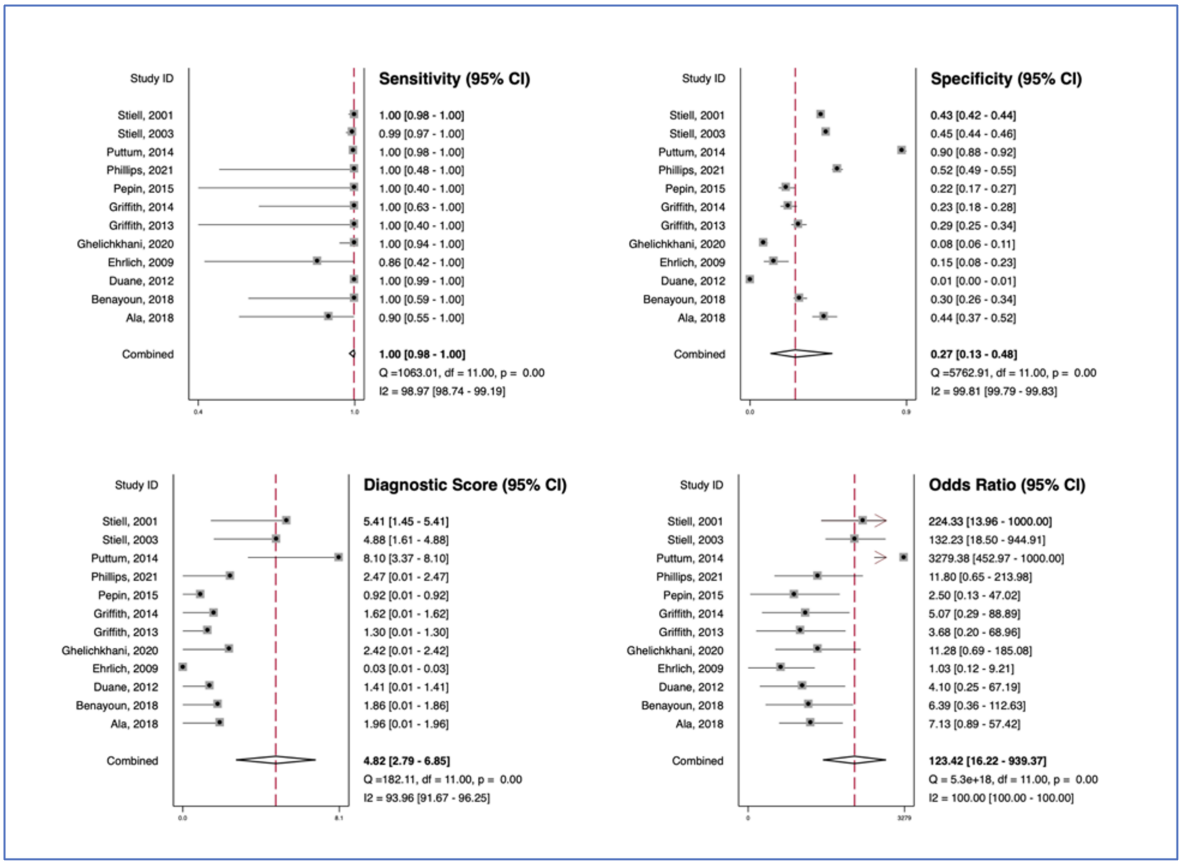
Supplementary Figure 6: Sensitivity, specificity, and diagnostic odds ratio of NEXUS in detection of any cervical spine injury in pediatric patients. CI: confidence interval.



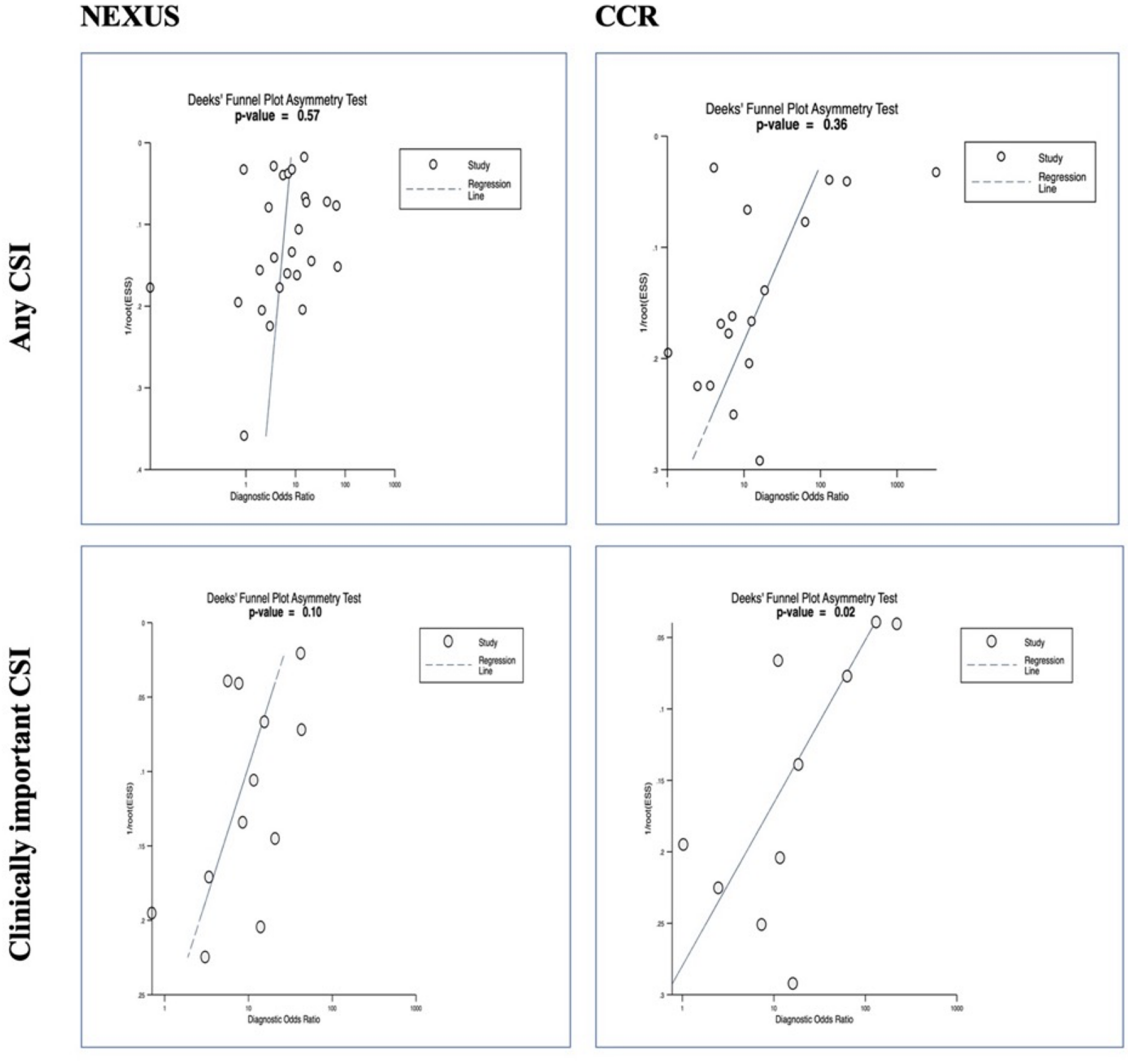
Supplementary Figure 7: Area under the receiver operating characteristic curve of NEXUS and CCR in detection of any cervical spine injury in direct assessment studies.



Supplementary Figure 8: Sensitivity, specificity, and diagnostic odds ratio of NEXUS in detection of any cervical spine injury in direct assessment studies. CI: confidence interval.



Supplementary Figure 9: Sensitivity, specificity, and diagnostic odds ratio of CCR in detection of any cervical spine injury in direct assessment studies. CI: confidence interval.



Supplementary Figure 10: Publication bias for included studies investigating performance values in any cervical spine injury (CSI) and clinically important CSI.