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The benefits and clinical application of the digital rectal exam in trauma populations: Towards enhancing patient safety and quality outcomes

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ABSTRACT

Introduction: Current literature contains an extensive number of analyses on the diagnostic value and utilization of the direct rectal exam in trauma patients. Presently, ATLS recommends the application of the digital rectal exam in trauma patients following a primary assessment of traumatic injuries. We aim to assess the validity and diagnostic value of the digital rectal exam in trauma populations.

Methods: PubMed, Google Scholar, EMBASE, ProQuest, and CINAHL databases were searched for studies from the date of database conception to August 6th, 2022. Studies that assessed the validity of the digital rectal exam performed in the emergency department or trauma bay, in both adult and pediatric trauma patients were included. Study outcomes and measurements of validity were summarized and compared.

Results: A total of 9 studies met inclusion criteria for both adult and pediatric trauma populations. The sensitivity of the digital rectal exam in detecting both spinal cord and urethral injuries in adult trauma populations ranged from 0 to 50%, while the sensitivity in detecting gastrointestinal injuries ranged from 0% to 51%. When compared to other clinical indicators, the digital rectal exam was consistently worse at detecting injuries. Within the pediatric trauma populations, the digital rectal exam resulted in high false negative rates ranging from 66% to 100%, failing to detect all urethral and gastrointestinal injuries and pelvic fractures.

Conclusion: The use of digital rectal exams in trauma patients illustrates limited to no validity and reliability in assessing pertinent injuries and does not influence the management of injuries. Trauma societies should consider creating guidelines and algorithms to clarify the use of digital rectal exams in specific situations and injury types.

1. Introduction

The digital rectal exam (DRE) is a commonly incorporated physical exam utilized in the secondary assessment of incoming trauma patients [1]. Recommended by the American College of Surgeons Advanced Trauma Life Support course (ATLS), the DRE's intention is to assess for a decreased or absent rectal tone, gross blood, a "high-riding" prostate, palpation of bony fragments, or a disruption of the rectal wall [1]. These findings can act as positive or negative indicators that can assist physicians in determining whether a spinal cord injury, urethral disruption, or pelvic fracture has occurred. However, while recommended by the ATLS, this examination has received infrequent support throughout the emergency medicine community as it is highly uncomfortable for the patient, easily misinterpretable, and potentially unreliable [2].

Metrics such as sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) are commonly utilized to gauge the validity of examinations in clinical practice. However, recent scientific literature has observed unfavorable results following the usage of the DRE. Specifically, Esposito et al. analyzed the functionality of the DRE relative to other clinical indicators (OCI) gathered throughout the course of a trauma evaluation [3]. The DRE was examined with respect to its ability to predict three "index injuries": urethral disruption, spinal cord injury (SCI), and gastrointestinal (GI) bleeding [3]. The DRE had a PPV of 27% and an NPV of 99% for all injuries evaluated [2]. Furthermore, Shlamovitz et al. evaluated

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the validity of the DRE in 213 pediatric trauma patients, of which 6% had bowel injuries, 6% had pelvic fractures, 2% had rectal injuries, 1% had spinal cord injuries, and 0.5% had a urethral disruption [4]. The sensitivity of DRE for spinal cord injuries was concluded to be 33% while for all other diagnoses 0% [4].

Current literature has argued against the diagnostic value and utilization of the DRE in trauma patients; however, this sentiment is not agreed upon by the entire scientific community. The ATLS still recommends the utilization of the DRE in trauma patients following a primary assessment of traumatic injuries, but we were unable to locate any other governing medical society or regulatory bodies that support such practices. Therefore, the purpose of this systematic review is to assess the validity, clinical relevance, and diagnostic value of the digital rectal exam in adult and pediatric trauma populations to provide recommendations on its usage, functionality, and management practices for the future.

1.1. Population, Intervention, Comparator, and Outcomes (PICO)

PICO 1: In adult and pediatric trauma patients, what is the sensitivity of detecting spinal cord, gastrointestinal and urethral injuries when performing a digital rectal exam?

PICO 2: In adult and pediatric trauma patients, does performing a digital rectal exam change the treatment/management of spinal cord, gastrointestinal or urethral injuries?

2. Methods

A literature search of relevant articles was conducted utilizing PubMed, Google Scholar, EMBASE, ProQuest, and CINAHL from database inception through August 6th, 2022. Articles were initially searched and screened for relevance by all authors. Selected articles were further analyzed and reviewed by all authors. The search included the keywords “digital rectal exam” AND “trauma” OR “digital rectal exam” AND “trauma” AND “validity” OR “digital rectal exam” AND “adult” AND “trauma” OR “digital rectal exam” AND “pediatric” AND “trauma” OR “digital rectal exam” AND “trauma” AND “reliability” OR “digital rectal exam” AND “trauma” AND “outcomes”.

This review included studies that assessed the utilization of DRE performed in the emergency department or trauma bay, included either adult or pediatric trauma populations, measured the validity of DRE in detecting injuries later confirmed through diagnostic measures, included blunt and/or penetrating injuries, and were written in English. Exclusion criteria included studies that did not examine trauma populations, reported DRE usage without providing any additional information on its validity in detecting traumatic injuries, assessed the use of DRE that was performed outside of the emergency department or trauma bay, and were not written in English.

3. Results

The search resulted in 3810 initial articles, after removing duplicates, screening relevant abstracts and titles, and full-text reviews applying our inclusion and exclusion criteria, 9 articles remained and were included in this study. A diagram of the data search can be found in Fig. 1. From the 9 a total of 3775 patients had findings from a digital rectal exam [3-11]. 7 studies included adult populations [3-9] and 2 studies included only pediatric populations [10,11]. Demographic data of included studies are outlined in Table 1.

3.1. Digital rectal exam use in adult trauma patients - All injuries

The DRE appears to have limited benefit and validity in detecting acute traumatic injuries within adult trauma populations [3-6]. Docimo et al. investigated the use of DRE in 75 patients with traumatic injuries that were later confirmed via imaging [5]. The DRE proved useful in diagnosing 5 of the 75 injuries, with a sensitivity of 6.7%. Additionally, 2 of 39 injuries confirmed by exploratory laparotomy were detected by DRE, a sensitivity of 5.1% [5]. Ahl et al. found the sensitivity of the DRE to be 47% among adult patients with blunt injuries [6]. Furthermore, Shlamovitz et al. investigated 1401 trauma patients and found poor sensitivity of just 22.9% for detecting any traumatic injury [4]. In addition, the DRE was unable to detect 63% of spinal cord injuries, 94% of bowel injuries, 67% of rectal wall injuries, 100% of pelvic fractures, and 80% of urethral disruption injuries, further demonstrating that the exam provides no benefit in the trauma setting [4]. **(**Table 2A**).**

3.2. Digital rectal exam use in adult trauma patients - Spinal cord injuries

The DRE appears to have low validity and reliability in the detection of SCI in adult trauma patients [3,4,7]. Guldner et al. examined the validity of DRE in detecting spinal cord injuries in 1032 adult trauma patients [7]. The sensitivity was 50%, and only ~30% of patients with abnormal findings of a DRE had a SCI [7]. Indicating that most patients with decreased rectal tone on DRE will not truly have a SCI.

Docimo et al. found the sensitivity of DRE in detecting SCI in adult trauma patients to be 8.3% [5]. This is concerning due to the high prevalence of SCI which composed 21.62% of all injuries included in their study. Shlamovitz et al. analyzed close to 1400 trauma patients and found the sensitivity in detecting SCI to be 37% [4]. **(**Table 2B**).**

3.3. Digital rectal exam use in adult trauma patients - Gastrointestinal injuries

DRE has been shown to poorly assist in diagnosing GI injuries due to its low sensitivity [3,5,8]. Other diagnostic methods, such as rectal sigmoidoscopy (RS) have shown increased validity and reliability in screening for GI injuries [3]. Hargraves et al. compared DRE versus rectal sigmoidoscopy in detecting full-thickness penetrating rectal injuries and found the sensitivities to be 51% and 78% respectively, demonstrating the superiority of RS over DRE as a valid diagnostic tool for GI injuries [8].

Furthermore, when compared to other clinical indicators such as visible penetrating wounds to the abdomen, perineum, or rectum, and an unstable pelvis, the sensitivity of the DRE was much lower for detecting GI injuries than other clinical indicators, 36%, and 73% respectively [3]. Additionally, of the 11 GI injuries included in the study, 7 (63%) had negative findings on DRE. Conversely, other clinical indicators returned only 3 (27%) false-negative results of GI injuries [3]. Docimo et al. investigated 111 patients stratified by injury location [5]. It was found that colon injuries recorded the worst sensitivity (0%) among all injury types [5]. In comparison, small bowel injuries recorded a 6.90% sensitivity and rectal injuries provided the best sensitivity at 33% [5]. **(**Table 2C**).**

3.4. Digital rectal exam use in adult trauma patients - Urethral injuries

Traumatic urethral injuries have been poorly detected by DRE with among the lowest sensitivity rates of all DRE-identifiable injuries [5,9]. Ball et al. analyzed the sensitivity of DREs in detecting urethral disruption [9]. Of the 41 patients, only 1 patient was correctly diagnosed via DRE, with a sensitivity of 2% [9]. Similarly, Esposito et al. compared sensitivities of DRE versus other clinical indicators such as blood at the meatus and hematuria [3]. The accuracy of detecting a urethral disruption in DRE was 50% while the other clinical indicators yielded 100%.

The inability to reliably detect urethral injuries was further confirmed by Docimo et al. [5] A total of 111 patient profiles that had both DRE documentation along with confirmed radiological findings were included in the study. Among all injury types, urethral injuries had the worst sensitivity (0%). In addition, urethral injuries recorded a PPV of 0%, further demonstrating the poor validity of this exam [5]. **(**Table 2D**).**

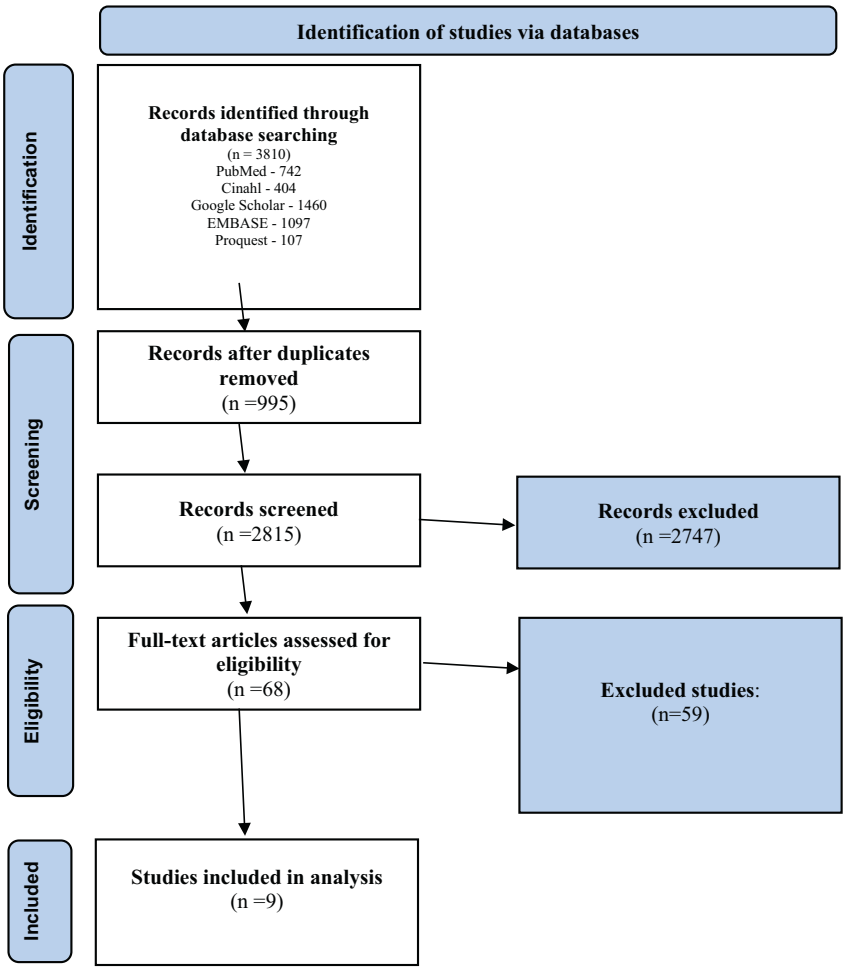

Fig. 1. PRISMA Flow Diagram of Included Studies in the Narrative Review.

3.5. Digital rectal exam vs other clinical indicators in adult trauma patients

The validity of DRE in diagnosing injuries may be worse in detecting injuries compared to other clinical indicators on the initial exam such as wounds around the umbilicus, visible penetrating wounds to the abdomen, buttock, or perineum, blood at the urethral meatus, neurologic deficit below the waist, scrotal hematoma, unstable pelvis, and others [3].

Esposito et al. compared the validity of DRE to that of other clinical indicators in 512 patients [3]. The overall accuracy of DREs in detecting these injuries was only 41%. Comparatively, the overall accuracy of other clinical indicators was 73%. When these other clinical findings were absent, DRE findings were also absent in all of the confirmed index injury cases. Other clinical indicators missed six index injuries yielding a false negative rate of 22%. DRE missed 17 index injuries for a false-negative rate of 63% [3]. Additionally, the DRE provided no additional information in 85% and changed management in only 11% [3]. Further demonstrating that the DRE does not provide any additional benefit in screening trauma patients for injuries upon initial presentation.

Table 1
Demographic data of studies included in the review.

	Study demographics							
Study (Year)	Study design	Country	Level of Trauma Center(s)	Total (n)	Age (mean)	Gender (%male)	Injury Severity Score mean (SD) [median (IQR]	Mechanism: Blunt and/or Penetrating
Esposito et al. (2005)	Prospective Study	US	Level 1	512	2 months - 102 years	72%	12	Blunt and Penetrating
Hargraves et al. (2009)	Retrospective Study	US	Level 1	77	31 years	91%	15	Penetrating
Ahl et al. (2016)	Retrospective Study	Sweden	NR	253	44 years	75%	26 ± 16	Blunt and Penetrating
Guldner et al. (2006)	Retrospective Study	US	Level 1	1032	NR	NR	NR	NR
Kristinsson et al. (2004)	Pilot Study	US	Level 1	135	12 years	71%	NR	NR
Docimo et al. (2015)	Retrospective Study	US	Level 1	111	37.7 years	82.8%	NR	NR
Ball et al. (2009)	Retrospective Study	US	Level 1	41	38.5 years	100%	21 [4–54]	Blunt
Shlamovitz et al. (2007)	Retrospective Study	US	Level 1	1401	36.2 years	72%	NR	Blunt and Penetrating
Shlamovitz et al. (2007)	Observational Chart Review	US	Level 1	213	12.6 years	69%	NR	Blunt and Penetrating

Abbreviations: NR; not reported; SD; standard deviation; IQR; interquartile range.

Table 2A
Predictive outcomes of DRE use in studies that included both adult and pediatric trauma populations combined.

DRE in Adult Trauma Patients - Overall						
Study (Year)	Sensitivity	Specificity	PPV	NPV	False Negative Rates	False Positive Rates
Esposito et al. (2005)	40%	NR	27%	99%	63%	NR
Hargraves et al. (2009)	51%	NR	NR	NR	NR	NR
Ahl et al. (2016)	47%	NR	NR	NR	NR	NR
Docimo et al. (2015)	6.67%	94.44%	71.43%	32.69%	NR	NR
Shlamovitz et al. (2007)	22.9%	94.7%	NR	NR	NR	NR

Abbreviation: DRE; direct rectal exam; NR; not reported: PPV; positive predictive value: NPV; negative predictive value.

Performing a DRE in the setting of traumatic injury does not appear to alter the treatment management of the patient [6]. Ahl et al. compared the management of patients whose charts reported a DRE versus those that did not report a DRE on the initial exam [6]. Out of the 160 patients that had a DRE, only one was taken directly to the operating room, the rest were taken to get CT imaging. In the group that had no DRE on the initial exam, 12 patients were taken directly to the operating room and 83 were taken to get a CT. This indicates that most patients were taken to CT imaging regardless of their DRE findings and suggests that DRE does not play a pivotal role in immediate management decision-making in the trauma setting.

3.6. Digital rectal exam use in pediatric trauma patients

Our study indicates that the DRE does not provide any additional screening benefits in the pediatric trauma population. Kristinsson et al. investigated the validity of DRE in detecting injuries in 165 pediatric trauma patients [10]. Of the 8 patients that had DRE identifiable injuries, only 2 (25%) had positive findings on DRE. However, a total of 14 patients had positive findings on DRE and only 2 had a DRE identifiable injury, resulting in 85.7% of cases being false positive findings. In addition, performing a physical exam (PE) without a DRE provided equivalent validity in detecting traumatic injuries compared to a PE with a DRE. The sensitivity was 87.5% when a physical exam with and without a DRE was performed. However, the PPV was higher when performing a PE without a DRE (30.4%) than when including a DRE (20.6%) [10].

Similarly, Shlamovitz et al. found that among 213 pediatric trauma patients in which a DRE was performed, the DRE missed 66% of spinal cord injuries, 100% of urethral injuries, 100% of bowel injuries, 100% of rectal wall injuries, and 100% pelvic fractures [11]. Further demonstrating that the DRE provides no benefit in detecting injuries in pediatric trauma populations. **(**Table 3**).**

4. Discussion

This review included 9 studies evaluating the digital rectal exam as a screening tool in adult and/or pediatric trauma populations with spinal cord, gastrointestinal, or urethral injuries. In adults, it was found that DRE consistently had a poor sensitivity overall ranging from 6.67%–51% [3-6,8]. When assessing for spinal cord injuries, the sensitivity ranged from 8.3%–50% [3,4,6,7]. Similarly, gastrointestinal and urethral injuries had the worst sensitivities, ranging from 0 to 51% and 0–50% respectively [3-5,8,9]. In addition, using OCI to detect injuries proved to be more sensitive than performing a DRE with an accuracy of 73% and 41% respectively [3]. Furthermore, DRE findings dictated a change in management in only 11% of patients [3].

Within the pediatric trauma population, performing a DRE coupled with a PE did not increase the sensitivity of detecting injuries in comparison to performing a PE without it [10]. In addition only spinal cord injuries were detected in pediatric populations with a sensitivity of 66% [11]. Other injuries including GI, urethral and pelvic fractures, were missed 100% of the time [11]. These findings demonstrate that the DRE is associated with a low predictive value overall and for specific injuries, indicating that its use should therefore be re-evaluated.

When comparing the overall validity of DRE in detecting traumatic injuries to previous studies, our study revealed similar values as those seen in a 2004 retrospective case series of adult blunt trauma patients by Guldner et al. [12] In this case series, they found the DRE to have a PPV of 64%, however, it did not include sensitivity in the report. In comparison, our study provides a thorough analysis of DRE in trauma diagnosis including sensitivity, specificity, and PPV.

In spinal cord injuries, we found that the DRE had exceedingly poor predictive abilities with sensitivities ranging from 8.33 to 50% [3,4,6,7]. Similarly, a review conducted in 2009 concluded that DREs did not increase the probability of detecting spinal cord injuries [13], with sensitivities ranging from 33 to 50%. However, this review is not a peer-reviewed article weakening the results of its findings. In addition, our study includes more studies overall and more recent literature on the topic leading to stronger results.

In detecting gastrointestinal injuries, our findings demonstrated that the use of DRE had poor validity with sensitivities ranging from 0 to 51% [3-5,8]. Similarly, a review conducted by Quinn et al. concluded a limited sensitivity of the DRE in detecting GI injuries but failed to provide numerical values for sensitivity. In comparison [14], Our review includes more studies supported by the statistical values of the sensitivity of DRE, thereby strengthening our findings.

In detecting urethral injuries via the DRE, our findings demonstrated sensitivities ranging from 0 to 50% [3-5,9]. However, half of the studies found the sensitivity to be 2% or less, likely due to the difficulty in determining whether the prostate is high-riding or non-palpable which indicates possible injury to the urethra. In a study done by Johnson et al., they assessed the prostates of 100 individuals without any urethral injuries [15]. They found the prostate to be nonpalpable in 50% of

Table 2B
Predictive outcomes of DRE use in adult spinal cord injuries.

DRE in Adult Spinal Cord Injuries						
Study (Year)	Sensitivity	Specificity	PPV	NPV	False Negative Rates	False Positive Rates
Esposito et al. (2005)	36%	NR	47%	98%	NR	NR
Guldner et al. (2006)	50%	93%	27%	97%	NR	NR
Docimo et al. (2015)	8.33%	95.4%	NR	NR	NR	16.6%
Shlamovitz et al. (2007)	37%	95.7%	NR	NR	63%	NR

Abbreviations: DRE; direct rectal exam; NR; not reported: PPV; Positive Predictive Value: NPV; Negative Predictive Value.

Table 2C
Predictive outcomes of DRE use in adult gastrointestinal injuries.

DRE in Adult Gastrointestinal Injuries						
Study (Year)	Sensitivity	Specificity	PPV	NPV	False Negative Rates	False Positive Rates
Hargraves et al. (2009)	51%	NR	NR	NR	NR	NR
Esposito et al. (2006)	36%	NR	15%	97%	NR	NR
Docimo et al. (2015)	6.9% (SB) 0% (C) 33.33% (R)	100% (SB) 97.83% (C) 99.07% (R)	100% (SB) 0% (C) 50% (R)	75.23% (SB) 82.57% (C) 98.17% (R)	NR	NR
Shlamovitz et al. (2007)	5.7%	98.9%	NR	NR	94%	NR

Abbreviation: Abbreviations: DRE; direct rectal exam; NR; not reported: PPV; Positive Predictive Value: NPV; Negative Predictive Value: SB; Small Bowel: C; Colon: R; Rectum.

patients, further demonstrating that a nonpalpable prostate can be a common finding in patients without any history of traumatic injury, leading to decreased validity of the exam in trauma patients.

In addition, multiple studies concluded that the usage of DRE was not only a poor predictor to diagnose injuries, but rarely had an impact on dictating treatment [3,6]. It was found that the DRE dictated a change in the management of injuries in only 11% of patients [3]. Similarly, a clinical review of non-trauma patients conducted by Kessler et al. depicted an alteration in management only 7% of the time after a positive DRE [16]. Our findings provide evidence that the use of DRE does not significantly alter the management of acute injuries in trauma patients.

Within pediatric trauma patients, the DRE only detected 33% of spinal cord injuries and missed every urethral and GI injury and pelvic fracture [11]. In addition, performing a PE with a DRE proved to be just as sensitive in detecting injuries as a PE without it [10]. Our findings demonstrate that the DRE is not an effective tool in detecting injuries in pediatric trauma patients. To the best of our knowledge, no current review in the literature details the use of DRE among pediatric trauma populations.

Despite current studies indicating the exclusion of the DRE, the 2021 ATLS continues to include the use of DRE as part of the secondary survey to assess trauma injuries [1]. However, this review has clearly demonstrated the poor sensitivity of the DRE in detecting traumatic injuries and may provide enough evidence for the removal of DRE from current trauma assessment guidelines altogether or used only in specific situations and injury types.

Currently, other trauma societies do not provide specific management guidelines or algorithms relating to DRE in trauma populations. For example, the Western Trauma Association provides guidelines and algorithms on specific injuries such as blunt bowel injuries [17]. However, their algorithm for such injuries does not include the utilization of DRE, instead suggests the usage of clinical indications and imaging [17]. This review shows that greater sensitivities to detect DRE-related injuries are seen when using OCI compared to the DRE [3]. Therefore, this review can encourage the adoption of similar guidelines and algorithms in the ATLS and other trauma societies in order to provide more effective diagnostic outcomes.

Given the findings from this review, we offer several recommendations. First, given our findings that the sensitivity of the DRE in trauma patients is 50% or less, we recommend that the ATLS review their current guidelines and consider making the DRE an optional exam instead of mandatory in both adult and pediatric trauma patients. Next, if other trauma societies continue the recommendation of DRE use in their trauma guidelines for adult and pediatric populations, we suggest they limit its use to spinal injuries, considering our data had higher sensitivity values for these types of injuries, although they were still below 50%. The lack of guidelines regarding the use of DRE from trauma societies could possibly be contributing to the continued inclusion of DRE in the ATLS guidelines. Finally, given that our findings showed that performing a DRE does not change the management of injuries in trauma populations, we recommend hospital administrations consider creating their own policies regarding the use of DRE in screening traumatic injuries. Complete omission of the exam may aid in optimizing time in the management of the majority of traumatic injuries.

This review has several limitations. First, due to the dearth of literature on the topic only 9 studies were included in this review, none of which were randomized controlled trials. In addition, none of the studies stratified results by injury type thereby limiting our ability to draw conclusions about the value of DREs among blunt and penetrating types of injuries. Next, none of the studies had standardized methods of performing the DRE and across most of the studies, the exam could've been performed by a medical student, intern/resident, or attending, leading to potential discrepancies in the interpretation of the findings from the exam. Lastly, many studies recorded a very low incidence of specific injuries such as urethral disruption which limits the results of the validity calculations.

5. Conclusion

This review demonstrates that the sensitivity of the digital rectal exam in detecting all injuries within adult and pediatric trauma populations is 50% or less. The digital rectal exam was consistently worse in detecting injuries than other clinical indicators and it did not alter the next steps in the management of the majority of traumatic injuries. Future studies should investigate the validity of the digital rectal exam by addressing additional factors such as injury type and severity, and associated treatment outcomes. In addition, trauma societies should seriously consider creating guidelines to clarify the future use of digital rectal exams among trauma populations in specific situations and injury types.

Table 2D
Predictive outcomes of DRE use in Adult Urethral Injuries.

DRE in Adult Urethral Injuries						
Study (Year)	Sensitivity	Specificity	PPV	NPV	False Negative Rates	False Positive Rates
Ball et al. (2009)	2%	NR	NR	NR	NR	NR
Esposito et al. (2006)	50%	NR	33%	100%	NR	NR
Docimo et al. (2015)	0%	100%	0%	93.69%	NR	NR
Shlamovitz et al. (2007)	20%	99.5%	NR	NR	80%	NR

Abbreviations: DRE; direct rectal exam; NR; not reported: PPV; Positive Predictive Value: NPV; Negative Predictive Value.

Table 3
Predictive outcomes of DRE use in studies that only included pediatric trauma populations.

	DRE in Pediatric Trauma Patients				
Study (Year)	Sensitivity	Specificity	PPV	NPV	False Positive Rate
	PE + DRE: 87.5%	PE + DRE: 78.7%	PE + DRE: 20.6%	PE + DRE: 99.0%	
Kristinsson et al. (2004)	PE - DRE: 87.5%	PE - DRE: 87.4%	PE - DRE: 30.4%	PE - DRE: 99.1%	85.7%
Shlamovitz et al. (2007)	33% (SCI) 0%(GI) 0%(UD)	98% (SCI) 99%(GI) 100%(UD)	NR	NR	NR

Abbreviations: DRE; direct rectal exam; NR; not reported: PPV; Positive Predictive Value: NPV; Negative Predictive Value: PE; Physical Exam: SCI; Spinal Cord Injury: GI; Gastrointestinal Injury: UD; Urethral Disruption.

Author's contributions(s)

Study design and conceptualization, supervision and project adminstration: AE.

Data collection & curation, methodology and investigation, formal analysis: GB, NA, RZ, HW, AE.

Manuscript writing (original draft), review and editing: GB, NA, RZ, HW, AE.

All authors read and approved the final manuscript.

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CRediT authorship contribution statement

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