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Spontaneous Bladder Rupture: Demystifying the Condition – A Systematic Review

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A Research Report submitted to the Faculty of Health Sciences of the University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in Emergency Medicine

Johannesburg, 2023

DECLARATION

I, Deshin Reddy, Student No. 303672, hereby declare that this research report is my own work and has not been submitted or presented for any other degree or professional qualification at this or any other institute. This research was undertaken in the Division of Emergency Medicine, University of the Witwatersrand, Johannesburg, South Africa.

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PUBLISHED ARTICLE

Spontaneous (Idiopathic) Rupture of the Urinary Bladder: A Systematic Review of Case Series and Reports

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ABSTRACT

Objectives: To perform a systematic review of all cases of spontaneous rupture of the urinary bladder (SRUB) and to describe the demographic data, associated co-morbidities, clinical presentation, diagnosis, relevant laboratory findings, associated factors, management, morbidity, and mortality associated with the presentation of SRUB.

Methods: The study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO). A search was carried out across the following electronic databases: PubMed, Web of Science, Scopus, Google Scholar, and the Cochrane Database of Systematic Reviews. Full texts of selected studies were analysed, and data extracted. The review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Results: A total of 278 articles comprising 240 case reports and 38 case series, with a total of 351 patients were included. The median (IQR) age of all included patients was 47.5 (33-65) years. The median (IQR) time to presentation was 48 (24-96) hours, with the major presenting symptom being abdominal pain (76%). In patients in whom the diagnosis was made prior to any intervention, the condition was misdiagnosed in 64% of cases. The diagnosis was confirmed during explorative open surgery in 42% of cases. Pelvic radiation (13%) and alcohol intoxication (11%) were the most common associated factors. Intraperitoneal rupture (89%) was much more common with the dome of the bladder being most frequently involved (55%). The overall mortality was 15%.

Conclusion: This review identified a number of key factors that appear to be associated with an increased incidence of SRUB. It also emphasised the high rate of misdiagnosis and challenges in confirming the diagnosis. Overall, it highlighted the importance of the need for increased awareness and maintaining a high index of suspicion for this condition.

KEY WORDS

spontaneous bladder rupture, idiopathic bladder rupture, atraumatic bladder rupture, uroperitoneum, urinary ascites, pseudo-renal failure, SRUB, #Urology, #UroTrauma

INTRODUCTION

Rupture of the urinary bladder is a potentially life-threatening urological emergency requiring prompt diagnosis and treatment. The vast majority of cases of bladder rupture is secondary to bladder injury or trauma, however, in 3.4% of cases there is no prior history of trauma (1). In general, the diagnosis is rather challenging, placing this particular subset of patients at considerable risk due to time delays in definitive management (2). Much of the aetiology and risk factors associated with this condition appear to be poorly understood.

Spontaneous rupture of the urinary bladder (SRUB) is defined as perforation or rupture of the bladder in the absence of trauma or direct stimulation (3,4). This term also excludes cases where the rupture has occurred as a direct result or complication of instrumentation or previous bladder surgery, e.g., cystoscopy, transurethral resection of bladder tumour (TURBT).

Spontaneous rupture of the urinary bladder appears to be a relatively rare condition, with the incidence previously been described as 1:126 000 (5,6). Later studies have indicated that the actual incidence may be as high as 1:50 000 (7).

Despite the relatively low reported incidence of SRUB, the mortality rate appears to be significant, ranging from 47-80% (6,8). It seems that the risk of mortality may be somewhat related to the underlying undiagnosed condition associated with the bladder rupture (9,10). This systematic review aims to determine and describe the potential risk factors, other associated factors, diagnosis, management, morbidity, and mortality of patients with SRUB

METHODS

Protocol and ethics

The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) in March 2021 (registration ID: CRD42021232134). An ethics waiver (W-CBP-210323-01) was received from the University of Witwatersrand Human Research Ethics Committee (Clinical) in March 2021.

Search strategy

A search was carried out in November 2021 across the following sources: PubMed, Web of Science, Scopus, Google Scholar, and the Cochrane Database of Systematic Reviews.

Additionally, a backwards citation search (pearl referencing) was also performed on articles that were retrieved, to identify articles that were missed during the search of the above databases.

For the PubMed database search, the following Medical Subject Headings (MeSH) terms were verified and indexed in the search builder: “urinary bladder” and “rupture, spontaneous”. Once the search was executed, the following limits were applied: human species and English language. There was no time limit applied. Similarly, the search strategy for the Web of Science, Scopus and Google Scholar databases was conducted using the following terms: ‘urinary bladder’ AND ‘rupture’ AND ‘spontaneous’. The limits applied were the same as stated above for the PubMed database search. The Cochrane Library search strategy was carried out in the Systematic Review section. The all-text filter was used in conjunction with the above search terms and limits.

Inclusion and exclusion criteria

Studies were included if (i) they reported on SRUB, (ii) the full text was available in English and (iii) they were pertaining to human subjects. Studies were excluded if (i) there was any preceding history of trauma, (ii) there was a history of any known structural bladder abnormality or known bladder lesion (e.g., bladder malignancy or exstrophy), (iii) bladder rupture was secondary to a complication of a surgical procedure or a known medical condition, e.g. tubo-ovarian complex or appendicitis, (iv) there was a history of any instrumentation or bladder surgery that could have been directly linked to the rupture (e.g. augmentation, cystoscopy, neobladder, partial cystectomy, bladder stone removal or TURBT) (11,12), (v) intrapartum bladder rupture was a result of suspected traumatic vaginal delivery or as an iatrogenic complication during caesarean section, (vi) bladder rupture was diagnosed in the ante-natal period or presented during the neonatal period. Additionally, studies were also excluded in the event that an abstract did not contain all necessary information or the full-text was not available.

Study selection

Electronic search limits were first applied as part of the initial screening process. After removal of duplicates, an initial cursory abstract screening was thereafter carried out where irrelevant studies and studies where the full text was unavailable were removed. This was followed by a more thorough abstract screening where studies fulfilling exclusion criteria

were removed. Full text reports were thereafter reviewed. Exclusion criteria were again applied, thereafter resulting in the final number of studies included in the review **(Figure 1).**

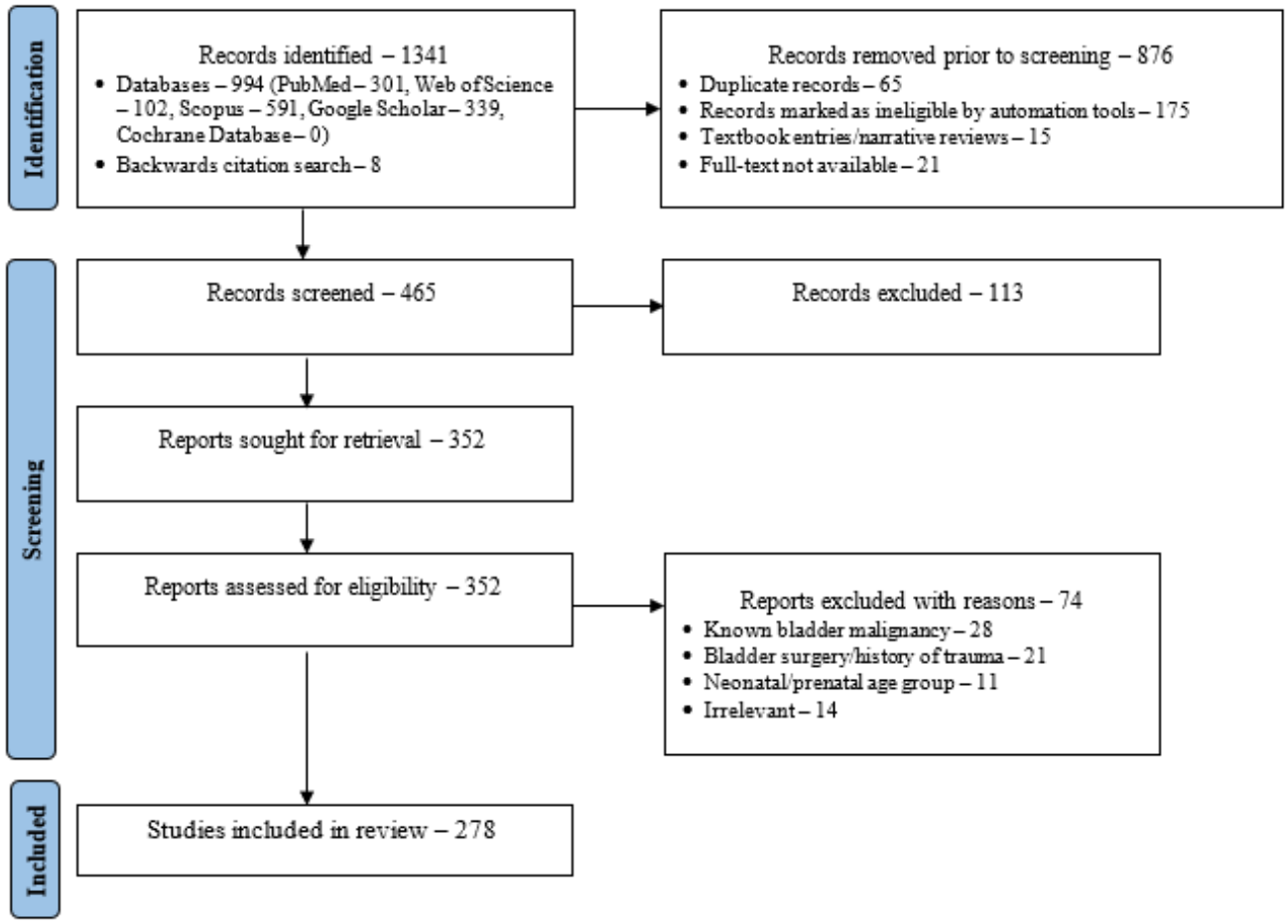


Figure 1: Study search strategy PRISMA flow diagram

Data extraction and methodology evaluation

The review was carried out using the framework outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Two reviewers independently screened the articles using eligibility and exclusion criteria (DR & AL). Any disagreements or uncertainties related to whether a study should be included were resolved by a third reviewer (AA). Data was extracted from individual studies and collated in an Excel spreadsheet (Microsoft Corporation, Redmond, WA, USA). Data for individual variables (gender, age, co-morbidities, clinical presentation, examination findings, diagnostic data, authors' assessment of exposure, serum laboratory parameters, management, and outcome) were tallied and represented as frequency and percentage. If data was not specified in the text, this was recorded as 'not specified'.

Assessment of methodological quality of the included studies

Since all studies meeting the inclusion criteria were case reports and case series, a modification to the tool proposed by Murad et al. (13) was used to assess the methodological quality of the included manuscripts. This modified tool has been utilised in several other systematic reviews of case reports (14,15) The original tool is comprised of four domains with eight questions in total. Since two of the questions pertain specifically to drug reactions, these were omitted. The included questions were as follows: 1) Does/do the patient(s) represent(s) the whole experience of the investigator or is the selection method unclear to the extent that other patients with similar presentation may not have been reported? 2) Was the condition adequately ascertained? 3) Was the outcome adequately ascertained? 4) Were other alternative causes that may explain the observation ruled out? 5) Was follow-up long enough for outcomes to occur? 6) Is/are the case(s) described with sufficient details to allow other investigators to replicate the research or to allow practitioners to make inferences related to their own practice?

The overall methodological quality of each of the included articles was described as either low, intermediate, or high quality. High quality was defined as a "yes" answer to four or more of the included questions, while intermediate quality was defined as a "yes" answer to three of the included questions and low quality was defined as a "yes" answer to less than three of the included questions **(Supplementary Table 1)**.

Data synthesis

The outcomes reported were summary data pertaining to the presentation of SRUB and included patient demographics, co-morbidities, clinical presentation, diagnosis, relevant laboratory findings, associated factors, site of bladder rupture, management, morbidity and mortality. Since all included studies were case reports, summative statistics and a narrative synthesis approach was primarily utilised to describe the findings.

RESULTS

The electronic search yielded a total of 1341 studies as follows: PubMed (301), Web of Science (102), Scopus (591), Google Scholar (339), Cochrane Database of Systematic Reviews (0) and, backwards citation search (pearl referencing) (8). Automatic search limits excluded 175 studies and a further 36 were removed as they were irrelevant. After duplicates were removed (665), a total of 465 abstracts were fully reviewed. Once exclusion criteria

were applied to the abstracts, 352 studies remained for full-text review. After again applying the exclusion criteria to the full-texts, a total of 278 manuscripts remained and were included in the final review (1–10,16–283). Details of the above are described in figure 1.

Design of the included publications

All included studies were either case reports (240) or case series (38) and comprised a total of 351 patients.

Demographics

The age range of all included patients was from 9 months to 91 years **(Supplementary Figure 1)**, with a median (interquartile range – IQR) age of 47.5 (33-65) years. There was a bimodal age distribution with peaks at 21-40 years and ≥60 years (111/331; 34% for both). This was followed by the 41–60-year-old age group (88/331; 27%) and the under 20-year-old age group (21/331; 6.3%). Of the total number of cases that specified gender, the distribution had a slight female predominance (n=173/331; 52%) **(Table 1)**.

Co-morbidities

A total of 153 (44%) patients had reported at least one co-morbid condition, with the most frequent co-morbidities being diabetes mellitus (n=21; 6.0%), cervical adenocarcinoma (n=21; 6.0%) and hypertension (n=15; 4.3%). The most common group of co-morbid conditions was cardiovascular-related disease (n=63; 18%), followed by malignancy (n=44; 13%). Most malignancies were pelvic in origin (n=40/44; 91%) **(Table 1)**.

Table 1: Demographic details, co-morbidities, time to presentation and diagnosis, laboratory variables, site of rupture, management and recurrence related to spontaneous rupture of the urinary bladder

	n (%) / median [IQR]
Sex (n=351)	
Male	158 (45)
Female	173 (49)
Unspecified	20 (5.7)
Age (n=331)	
Median age [IQR] (years)	47.5 [33-65]
< 20 years old	21 (6.3)
21-40 years old	111 (34)
41-60 years old	88 (27)
> 60 years old	111 (34)
Major co-morbidities (n=351)	
Co-morbid disease present	153 (44)
None	51 (15)

Not specified	147 (42)
Cardiovascular	63 (18)
Diabetes mellitus	21 (6.0)
Hypertension	15 (4.3)
Dyslipidaemia	7 (2.0)
CVA	7 (2.0)
Malignancy	44 (13)
Cervical cancer	21 (6.0)
Bladder cancer	5 (1.4)
Prostate cancer	4 (1.2)
Neurological	36 (10)
Paraplegia	10 (2.9)
Multiple sclerosis	7 (2.0)
Quadriplegia	3 (0.9)
Urological	35 (10)
BPH	11 (3.2)
Urolithiasis	9 (2.6)
Vesicolith	6 (1.7)
Psychiatric	12 (3.4)
Schizophrenia	5 (1.4)
Depression	3 (0.9)
Renal	9 (2.6)
Infection	8 (2.3)
Pulmonary	6 (1.7)
Genetic/autoimmune	7 (2.0)
Gynaecological	7 (2.0)
Rheumatological/orthopaedic	5 (1.4)
Other	12 (3.4)
Median time to presentation [IQR] (hours)	**48 [24-96]**
Serum laboratory parameters	
Median urea [IQR] (mmol/L)	21.5 [13.0-35.0]
Median creatinine [IQR] (μmol/L)	393.0 [199.8-590.8]
Peritoneal site of rupture (n=351)	
Intraperitoneal	314 (89)
Extraperitoneal	26 (7.4)
Not specified	11 (3.1)
Anatomical site of rupture (n=351)	
Dome	192 (55)
Posterior wall	48 (14)
Inferolateral wall	20 (5.7)
Anterior wall	14 (4.0)
Dome extending to posterior wall	5 (1.4)
Dome extending to anterior wall	1 (0.3)
Posterior wall extending to inferolateral wall	1 (0.3)
Not specified	70 (20)
Management (n=351)	
Open repair	249 (71)
Conservative	47 (13)
Laparoscopic repair	14 (4.0)
HBO	4 (1.1)
Cystectomy	2 (0.6)
Open repair + HBO	1 (0.3)
Demised prior to intervention (post-mortem)	12 (3.4)
Not specified	22 (6.3)
Management excluding cases diagnosed on laparotomy and post-mortem (n=195)	
Open repair	107 (55)
Conservative	47 (24)
Laparoscopic repair	14 (7.2)
HBO	4 (2.1)

Open repair + HBO	1 (0.5)
Not specified	22 (6.3)
Recurrence (n=18)	
Open repair	10 (55)
Conservative	7 (39)
Laparoscopic repair	1 (0.6)

IQR, interquartile range; ED, emergency department; CVA, cerebrovascular accident; HBO, hyperbaric oxygen.

Clinical presentation

The median (IQR) time to presentation was 48 (24-96) hours. The major presenting symptoms were abdominal pain (n=267; 76%), of which the majority was unspecified abdominal pain (n=128; 36%), followed by nausea and/or vomiting (n=79; 23%), abdominal distention (n=74; 21%), and acute urinary retention or difficulty voiding (n=63; 18%). Notably, urinary symptoms were present in almost three-quarters of patients (n=259; 74%). The most common examination findings were abdominal distention (n=131; 37%), abdominal tenderness (n=84; 24%) and fever (n=34; 9.7%). Of those in whom abdominal tenderness was reported, 34/84 (40%) had generalised peritonitis. Only one case study reported that abdominal examination was within normal limits **(Supplementary Table 2)**.

Diagnosis

The median (IQR) time to diagnosis was 48 (24-96) hours. Of those cases that reported on the relevant data, the diagnosis was made in the emergency department (ED) in 28/253 (11%) cases. In patients in whom the diagnosis was made prior to any intervention, the condition was misdiagnosed in 119/185 (64%) cases, with the most common misdiagnosis being hollow viscus perforation (n=41/119; 34%) **(Table 2)**.

The diagnosis was confirmed during explorative open surgery in 147 (42%) cases, which excludes cases where the diagnosis was made at autopsy (n=11; 3.1%). This was followed by cases where the diagnosis was confirmed by plain-film x-ray cystography (n=72; 21%) and CT with cystography (n=47; 13%) **(Table 2)**.

Table 2: Diagnostic data and morbidity & mortality related to spontaneous rupture of the urinary bladder

	n (%) / median [IQR]
Median time to diagnosis from presentation [IQR] (hours)	**48 [24-96]**
Diagnosis made (n=351)	

In emergency department	28 (8.0)
Outside of ED	225 (64)
Not specified	98 (28)
A diagnosis made prior to intervention	185 (53)
Incorrect	119/185 (64)
Correct	66/185 (36)
No diagnosis made prior to intervention	166 (47)
Misdiagnoses (n=119)	
Gastrointestinal	102 (86)
Hollow viscus perforation	41 (34)
Bowel obstruction	13 (11)
Acute peritonitis unspecified	10 (8.4)
Urological	12 (10)
Acute urinary retention	4 (3.4)
Urosepsis	3 (2.5)
Obstructive uropathy	2 (1.7)
Renal	14 (12)
Primary acute renal failure	12 (10)
Pyelonephritis	1 (0.8)
UTI not specified	1 (0.8)
Gynaecological/obstetrics	7 (5.9)
Recurrence of gynaecological malignancy	2 (1.7)
Ruptured/torsion of ovarian cyst	2 (1.7)
PV bleeding	1 (0.8)
Diagnostic modalities used to confirm diagnosis (n=351)	
Exploratory laparotomy	147 (42)
Plain-film cystography	72 (21)
CT with cystography	47 (13)
CT without cystography	26 (7.4)
Cystoscopy	23 (6.6)
Exploratory laparoscopy	11 (3.1)
Autopsy	11 (3.1)
Formal US	6 (1.7)
Plain-film IV pyelography	1 (0.3)
MRI pelvis	1 (0.3)
Tc-99m DTPA renography	1 (0.3)
Voiding cystourethrogram	1 (0.3)
Bladder doppler US	1 (0.3)
Data not available	3 (0.9)
Use of bedside US in ED (n=351)	
Yes	11 (3.1)
No	297 (85)
Not specified	43 (12)
Morbidity (n=351)	
No morbidity	124 (35)
Not specified	132 (38)
Total morbidities	95 (27)
Respiratory	8 (2.3)
Cardiac	2 (0.6)
Bowel/intra-abdominal organ	9 (2.6)
Gynaecological	3 (0.9)
Urological	19 (5.4)
Bladder-related complications (partial/ total cystectomy/ cystoplasty/ conduit)	8 (2.3)
Non-bladder related	6 (1.7)
Chronic catheterisation	5 (1.4)
Sepsis and related complications	9 (2.6)
Necrotising fasciitis	2 (0.6)
Wound complications	3 (0.9)

Metabolic	1 (0.3)
Recurrence	17 (4.8)
Single episode of recurrence	13 (3.7)
Multiple episodes of recurrence	4 (1.1)
Missed during surgical intervention	3 (0.9)
Failed conservative management	3 (0.9)
Survival and mortality (n=351)	
Survival to hospital discharge	225 (64)
Not specified	75 (21)
Total deaths	51 (15)
Time not specified	11 (3.1)
<3 days	15 (4.3)
3-7 days	8 (2.3)
8-31 days	11 (3.1)
1-6 months	5 (1.4)
>6 months	1 (0.3)

UTI, urinary tract infection; PV, per vagina; CT, computed tomography; US, ultrasonography; IV, intravenous; Tc-99m, Technetium-99m; MRI, magnetic resonance imaging; DTPA, diethylenetriamine penta-acetate; IQR, interquartile range; ED, emergency department; HBO, hyperbaric oxygen.

Median urea and creatinine

The median (IQR) serum urea and creatinine levels were 21.5 (13-35) mmol/L and 393 (200-591) µmol/L, respectively **(Table 1)**. A total of 12 (3.4%) patients were misdiagnosed with primary acute renal failure and received renal replacement therapy **(Table 2).**

Associated factors

Rupture was considered idiopathic in 79 (23%) cases, where no exposure could be clearly identified. The most common associated factors related to SRUB were pelvic radiation (n=45; 13%) followed by alcohol intoxication (n=39; 11%) and post vaginal delivery (n=25; 7.1%).

The most common associated factors in the two most prevalent age groups were alcohol intoxication (n=26/111; 23%) in the 21-40 years age group and pelvic radiation (n=23/111; 21%) in the older than 60-year-age group. Where the exposure was deemed to be infection or inflammation-related, *Mycobacterium tuberculosis* (TB) was the most prevalent causative agent (n=10/49; 20%) **(Table 3)**.

Table 3: Cumulative incidence of factors associated with spontaneous rupture of the urinary bladder†

Factors associated with bladder rupture (n=351)	**n (%)**
Bladder outlet obstruction	44 (13)
Intravesical	10 (2.8)
Vesicolith	9 (2.6)

Bladder neck papilloma	1 (0.3)
Extravesical	34 (9.7)
Urological	27 (7.7)
Prostatic enlargement	17 (4.8)
BPH	16 (4.6)
Prostate cancer	1 (0.3)
Urethral catheterisation	6 (1.7)
Urethral stricture	4 (1.1)
Non-urological	7 (2.0)
Uterine fibroids/adenomyosis	2 (0.6)
Faecal impaction	2 (0.6)
Pelvic organ prolapse	3 (0.9)
Type not specified	5 (1.4)
Pregnancy associated	32 (9.1)
Post NVD	25 (7.1)
Intrapartum	5 (1.4)
Other	2 (0.6)
Infection/inflammation	49 (14)
Cystitis uncertain/unspecified origin	11 (3.1)
TB	10 (2.8)
Fungal	7 (2.0)
Parasitic	6 (1.7)
Bacterial (non-TB)	5 (1.4)
Gangrenous/necrotising	4 (1.1)
Eosinophilic	2 (0.6)
Granulomatous (non-TB)	2 (0.6)
Viral	1 (0.3)
Interstitial	1 (0.3)
Over-distention/delayed voiding	69 (20)
Drug-associated	46 (13)
Alcohol	39 (11)
Anticholinergic	4 (1.1)
Benzodiazepine	1 (0.3)
Opioid	1 (0.3)
Drug not specified	1 (0.3)
Non-drug associated	23 (6.6)
Neurogenic bladder	23 (6.6)
Increased IAP	2 (0.6)
Vomiting	1 (0.3)
Seizures	1 (0.3)
Bladder wall lesion	88 (24)
Malignancy associated	67 (19)
Radiation-associated fibrosis (pelvic malignancies of non-bladder origin)	45 (13)
Bladder TCC	10 (2.8)
Bladder SCC	7 (2.0)
Bladder unspecified type	4 (1.1)
Bladder leiomyosarcoma	1 (0.3)
Non-malignancy associated	19 (5.4)
Bladder diverticulum	17 (4.8)
Bladder amyloidosis	1 (0.3)
Fatty infiltration of bladder	1 (0.3)
Other	2 (0.6)
Warfarin toxicity	1 (0.3)
Haemophilia	1 (0.3)
Not identified (idiopathic)	79 (23)
Top 5 associated factors stratified by age group	
<20-year age group (n=21)	
Bladder diverticulum	3 (14)

BOO (UO)	3 (14)
Neurogenic bladder	3 (14)
Alcohol intoxication	3 (14)
Idiopathic	2 (9.5)
21–40-year age group (n=111)	
Alcohol intoxication	26 (23)
Post NVD	21 (19)
Idiopathic	13 (12)
Cystitis (TB)	8 (7.2)
Neurogenic bladder	7 (6.3)
41-60-year age group (n=88)	
Idiopathic	15 (17)
Neurogenic bladder	14 (16)
Alcohol intoxication	12 (14)
Pelvic radiation	10 (11)
Bladder diverticulum	7 (7.8)
>60-year age group (n=111)	
Pelvic radiation	23 (21)
BOO (BPH)	15 (14)
Bladder diverticulum	14 (13)
Idiopathic	10 (9.0)
Neurogenic bladder	10 (9.0)

BPH, benign prostatic hypertrophy; NVD, normal vaginal delivery; TB, tuberculosis; IAP, intra- abdominal pressure; TCC, transitional cell carcinoma; SCC, squamous cell carcinoma; BOO, bladder outlet obstruction; UO, unknown origin.
[†]Not all authors reported on the presence or absence of all associated factors. Hence, it is possible that a patient may have had some associated factors that were not reported.

Site of bladder rupture

Intraperitoneal rupture (n=314; 89%) was much more common than extraperitoneal rupture (n=26; 7.4%), with the dome of the bladder being most frequently involved (n=192; 55%) **(Table 1)**.

Management

Most patients were managed with open repair (n=249; 71%), followed by conservative management with catheterisation on free drainage (n=47; 13%). A total of 14 (4.0%) patients underwent laparoscopic repair. After excluding patients who were incidentally diagnosed with SRUB during exploratory laparotomy (n=156, 44%), 107/195 (55%) patients were managed with open repair and 47/195 (24%) were managed conservatively. Overall, the rate of recurrence was higher with conservative management (n=7/30; 23%) compared to open repair (n=10/147; 6.8%) **(Table 1)**.

Morbidity

The overall number of reported morbidities was 95 (27%), with the most common morbidity

being rupture recurrence (17/351; 4.8%); most of which were single episodes. This was followed by sepsis or sepsis-related complications (n=9; 2.6%), intra-abdominal organ complications (n=9; 2.6%), respiratory tract complications (n=8, 2.3%) and other bladder-related (non-recurrence) complications (n=8, 2.3%) **(Table 2)**.

Mortality

The overall number of reported deaths was 51 (15%). Most deaths occurred within 72 hours of presentation (n=15/51; 29%) **(Table 2)**. A total of 13 (3.7%) patients demised prior to the correct diagnosis or intervention (i.e., the cause of death was determined at autopsy). A total of 38 (11%) patients demised despite intervention.

DISCUSSION

Spontaneous rupture of the urinary bladder appears to be a disease that predominantly affects young adults and the elderly **(Table 1)**, with an almost equal incidence among males and females. The incidence of co- morbidities reflects the underlying factors related to SRUB. The major co-morbid disease found was diabetes mellitus which is likely associated with some degree of autonomic bladder neuropathy (284). There was also a high incidence of extra-vesical pelvic organ malignancy with all of these patients having received pelvic radiation.

The major presenting symptoms were abdominal pain, which was predominantly localised to the lower abdomen followed by nausea and vomiting, abdominal distention, and difficulty in passing urine or acute urinary retention. Patients with ascites and abdominal distention in the setting of acute onset abdominal pain should have this diagnosis excluded, particularly those with concomitant urinary symptoms.

The underlying pathogenesis of SRUB has previously been attributed to a predisposition of compromised bladder wall integrity in combination with increased intravesical pressure and/or increased intra-abdominal pressure (223). Radiation exposure was well noted as a cause of spontaneous bladder rupture in the literature (169,241). This is likely due to the effects of radiation cystitis where the initial mucosal insult of oedema and hyperaemia culminates in fibrosis and loss of bladder wall integrity (285). It is important to note that these patients can present with SRUB many years after treatment has been completed (169,241,259). Hence, the diagnosis of SRUB should always be considered in patients with a

past medical history of pelvic radiation.

Alcohol intoxication was found to be the second most common exposure in this review **(Table 3)**. The pathogenesis is thought to be secondary to alcohol-induced diuresis leading to increased intra-vesical pressure coupled with impaired awareness of bladder filling and the need to void (8). There may be significant overlap here between traumatic bladder rupture and SRUB, since intoxicated patients are less reliable historians and may not recall a history of trauma. Conversely, in patients presenting with abdominal pain and particularly those with urinary symptoms several days after an alcohol binge, consideration must be given to SRUB as part of the differential diagnosis.

Having undergone normal vaginal delivery was the third most prevalent associated factor **(Table 3)**. Again, this diagnosis may be easily missed and attributed to other more likely pathologies (250). It is important to note the risk of SRUB is increased when the bladder is not emptied prior to delivery and where there is perineal trauma leading to a degree of bladder outlet obstruction and urinary retention (38). A review of SRUB in pregnancy and the puerperium found that the majority (70%) occurred during normal vaginal delivery (250).

Neurogenic bladder was found to be among the five most prevalent associated factors across all age groups **(Table 3)**. Due to neurological dysfunction, these patients may not present with typical features of abdominal pain. Additionally, the bladder wall is often compromised in these patients, e.g. diverticulae or chronic inflammation, which places them at further risk of spontaneous rupture. Furthermore, many of these patients also harbour chronic indwelling urinary catheters which also contributes to bladder wall inflammation and rupture (33) as well as bowel erosion with resultant fistula formation (286). It is also important to consider the diagnosis of SRUB in cases where patients with chronic neurological conditions may not yet have been formally diagnosed with a neurogenic bladder, e.g. previous cerebrovascular event, diabetes mellitus, multiple sclerosis.

The diagnosis of SRUB was largely made during explorative surgery **(Table 2)**. To date, there have been no studies that have attempted to describe the gold-standard diagnostic modality, hence, evidence from the trauma literature has been used as a guide. Computed tomography (CT) without cystography has a low specificity in the diagnosis of traumatic bladder rupture (61%) compared to that of plain-film retrograde cystography (96%) (287).

Previously retrograde cystography was considered the gold-standard diagnostic modality for traumatic bladder rupture, but this has since shifted to CT cystography which has shown comparable specificity (288). CT has the distinct advantage of being less invasive than conventional cystography, easier to perform and is able to detect other intra-abdominal pathology while excluding bladder rupture (8). With the continued growth in use of point-of-care ultrasound in the emergency department, there appears to be some promise in its utility (47) and there is potential for further studies to investigate ultrasonographic signs and techniques to aid in making the diagnosis in the emergency department.

A low index of suspicion and the non-specific clinical presentation are likely the major contributing factors to the high rate of misdiagnosis associated with SRUB. Another confounding issue contributing to the misdiagnosis of SRUB is the peritoneal reabsorption of urea and creatinine that has escaped through the bladder wall defect leading to elevated serum readings when laboratory investigations are performed. These results may easily be misinterpreted as renal failure (30,31,52,71,75,77,88,94,95,103,156,179,180,233) which is further confounded by presentation with oliguria or anuria (143,168,183), leading to the initiation of renal replacement therapy. When the diagnosis is made reasonably early and the defect repaired or bladder drained to allow sufficient healing to occur, the levels of urea and creatinine generally resolve spontaneously within 24 hours (179). It is important to note that although there is no initial insult to the kidneys, if the diagnosis is delayed this may lead to acute kidney injury and associated life-threatening complications including electrolyte abnormalities (144).

The dome of the bladder is anatomically the most vulnerable region. As the bladder distends, the dome stretches resulting in a thinner wall, it also rises above the pelvis and away from the support offered by the bony pelvic structures, thereby making the bladder dome more prone to SRUB (175).

In many cases where open repair was performed, the patient was taken for an exploratory laparotomy where SRUB was an incidental finding (272,274,279,280). After excluding patients who were incidentally diagnosed with SRUB at exploratory laparotomy, a higher proportion of patients were managed conservatively (47/195; 24% vs 47/351; 13%). This is likely a better reflection of the actual management related to this condition. Very few studies described successful management with laparoscopic surgery (49,122,263,270). Laparoscopic

repair in the hands of an experienced surgeon may be a better option but this remains to be validated by the evidence.

There is a lack of literature related to the mortality associated with SRUB. In this review, the overall mortality rate, where reported, was 51/276 (18%), with the highest number of deaths (15/51; 29%) occurring within 72 hours of presentation. This underscores the need to make the diagnosis in a timely manner so definitive management may be implemented.

A limitation of this study relates to the heterogenous nature of case reports in general. Case reports are often fraught with inconsistencies and bias, which may lead to inaccuracies when pooling data from multiples sources. For example, estimates of proportions reported in this paper are expected to be inaccurate due to publication bias or reporting inconsistencies, hence, these should be taken as a guide only. For example, case reports with death as an outcome may be more likely to be written-up and published, leading to an overestimate of the actual mortality of SRUB. Conversely, non-systematic reporting of associated features of SRUB such as pelvic radiation or alcohol intoxication may have resulted in an underestimation of these factors, e.g., some reports may not have mentioned these despite them being present. Comprehensive registration and reporting of cases would give a more accurate approximation, but this is challenging for such a rare presentation.

In the past, there were few guidelines available to guide authors on the content of case reports to provide a measure of standardisation. This has since improved with the introduction of several widely accepted tools such as the tool by Murad et al. (13) and the CARE (CAse REport) guidelines (289). The hope is that as the use of such tools becomes more common practice, reporting on rare diseases will also become more standardised.

There were missing data points in some of the included manuscripts. These were reported as “not specified” in the study summary results and were excluded from individual analyses, which is the reason for the smaller denominators for some variables.

Possible examples of studies include prospective cohort studies to determine if certain exposures are indeed causally linked to development of this condition and clinical trials to determine what modalities are best in terms of diagnosis and treatment, as much of the current evidence related to bladder rupture originates from the trauma literature.

In conclusion, this review identified a number of key factors across different age groups that appear to be associated with an increased incidence of SRUB. It also emphasised the high rate of misdiagnosis and challenges encountered in confirming the diagnosis. Overall, this study highlights the importance of maintaining a high index of suspicion for SRUB in the appropriate patient. However, a number of important gaps were also identified as potential targets for future research. In light of these findings, healthcare professionals should be educated about the clinical manifestations and risk factors of SRUB. Developing enhanced diagnostic approaches, including imaging techniques and clinical algorithms, is crucial to improve accuracy and reduce misdiagnosis rates.

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The authors hereby certify that this submission is not under publication consideration elsewhere and is free from any conflict of interest.

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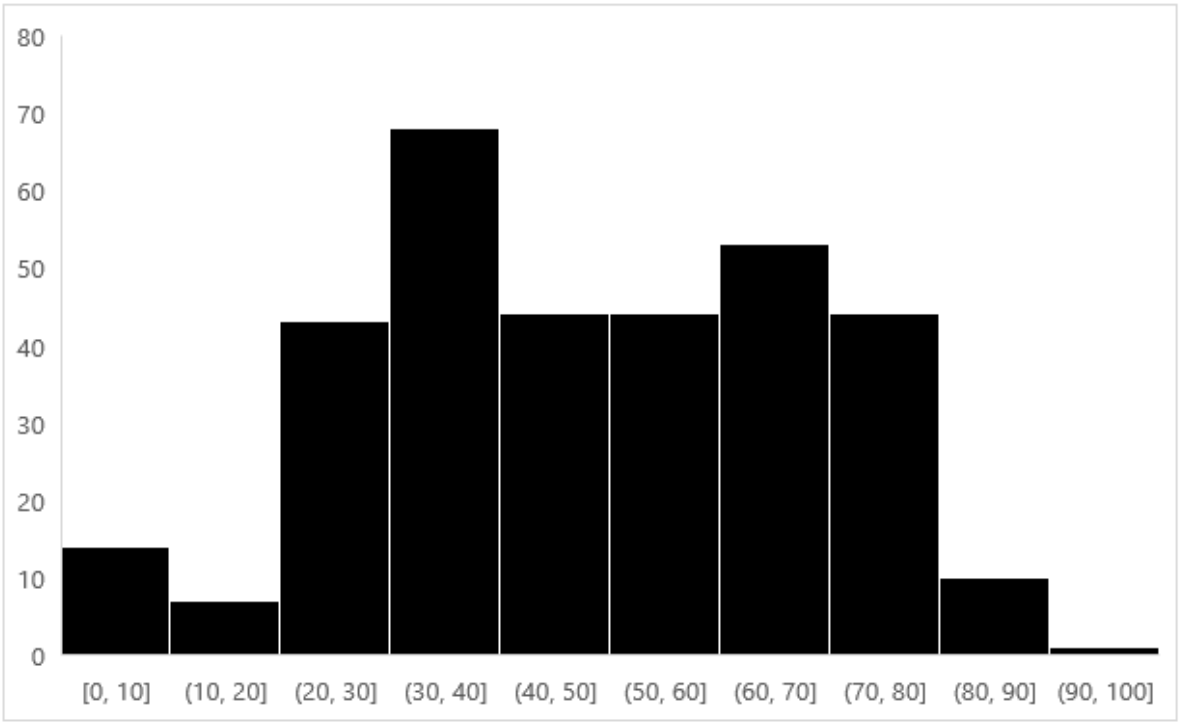
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SUPPLEMENTARY MATERIAL

SUPPLEMENTARY FIGURE



Supplementary Figure 1: Histogram of ages of patients presenting with spontaneous rupture of the urinary bladder (SRUB)

SUPPLEMENTARY TABLES

Supplementary Table 1: Methodological quality assessment of the included reports and series

Author	Selection	Ascertainment		Causality		Reporting	Overall
	Question 1	Question 2	Question 3	Question 4	Question 5	Question 6	Quality*
Ibrahimi et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Ouafidi et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Stabile et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Watanabe et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Zhang et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Raj et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Mukhtar et al.	Yes	No	Yes	Yes	Yes	Yes	High
Sholklapper et al.	Yes	No	Yes	Yes	Yes	Yes	High
Bergeron et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Ping	Yes	Yes	Yes	Yes	Yes	Yes	High
Modina et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Oh et al.	Yes	Yes	No	Yes	No	Yes	High
Marcos da Silva Barroso et al.	Yes	Yes	No	Yes	No	Yes	High
Asano et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Rahaman et al.	Yes	No	Yes	Yes	Yes	Yes	High

Elsaharty et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Welp et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Colombo et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Loganathan et al.	Yes	No	Yes	Yes	Yes	Yes	High
Magliolo et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Secrest et al.	Yes	Yes	No	Yes	Yes	Yes	High
Britto et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Sahin et al.	Yes	Yes	Yes	No	Yes	Yes	High
Chen et al.	Yes	Yes	No	Yes	No	Yes	High
Olanipekun et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Bierton et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Xu et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Chakraborty et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Monsellato et al.	Yes	No	Yes	Yes	Yes	Yes	High
Habek et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Qiao et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Palthe et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Alshareef et al.	Yes	No	Yes	Yes	Yes	Yes	High
Sung et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Murata et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Al Edwan et al.	Yes	Yes	No	No	No	Yes	Intermediate
Sharma et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Bourgeois et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Taniguchi et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Crawford et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Rawat et al.	Yes	Yes	Yes	No	Yes	Yes	High
Harada et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Hong et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Zhang et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Imataki et al.	Yes	Yes	No	Yes	No	Yes	High
Lua et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Raghavendran et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Mark et al.	Yes	No	Yes	Yes	Yes	Yes	High
Cekic et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Markou et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Zhao et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Farahzadi et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Zijoo et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Kodama et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Murray et al	Yes	Yes	Yes	Yes	Yes	Yes	High
Ioan et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Sawalmeh et al.	Yes	Yes	No	Yes	No	Yes	High
Sarma et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Inoue et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Mauerhofer et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Matsumura et al.	Yes	Yes	No	Yes	No	Yes	High
Uysal et al.	Yes	No	Yes	Yes	Yes	Yes	High
Kam et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Sharma et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Muneer et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Zhou et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Zhao et al.	Yes	No	Yes	Yes	Yes	Yes	High
Sabat et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Shin et al.	Yes	Yes	Yes	Yes	Yes	Yes	High

Kerigh et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Cusano et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Sailo et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Hariharasudhan et al.	Yes	No	Yes	No	Yes	Yes	High
Kivlin et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Hayashi et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Mardani et al.	Yes	Yes	No	Yes	No	Yes	High
Jairam et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Kawanami et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Wieloch et al.	Yes	No	Yes	Yes	Yes	Yes	High
Leahy et al.	Yes	Yes	No	Yes	No	Yes	High
Habek et al.	Yes	Yes	No	Yes	No	Yes	High
Nissi et al.	Yes	Yes	No	Yes	No	Yes	Intermediate
Dubey et al.	Yes	No	No	Yes	No	Yes	Intermediate
Huston et al.	Yes	Yes	Yes	No	Yes	Yes	High
Albino et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Hughes et al.	Yes	Yes	No	Yes	No	Yes	High
Snauwaert et al.	Yes	Yes	No	Yes	No	Yes	High
Al-Qassim et al.	Yes	No	No	Yes	No	Yes	Intermediate
Wong et al.	Yes	No	No	Yes	No	Yes	Intermediate
Limon et al.	Yes	Yes	No	Yes	No	Yes	High
Charalampidis et al.	Yes	Yes	No	No	No	Yes	High
Izumi et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Ridinger et al.	Yes	Yes	No	Yes	No	Yes	High
Su et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Daignault et al.	Yes	Yes	No	Yes	No	Yes	High
Galbraith et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Aber et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Gupta et al.	Yes	No	Yes	Yes	Yes	Yes	High
Mahfouz et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Ajape et al.	Yes	No	Yes	Yes	Yes	Yes	High
De Leon et al.	Yes	Yes	No	Yes	No	Yes	High
Gaikwad et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Kopp et al.	Yes	No	No	Yes	No	Yes	Intermediate
Li et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Mitchell et al.	Yes	Yes	No	Yes	No	Yes	High
Cornelis et al.	Yes	Yes	Yes	No	Yes	Yes	High
Goto et al.	Yes	No	Yes	Yes	Yes	Yes	High
Gupta et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Kong et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Sallami et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Chute et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Faraj et al.	Yes	Yes	No	Yes	No	Yes	High
Saleem et al.	Yes	Yes	No	Yes	No	Yes	High
Parker et al.	Yes	Yes	No	Yes	No	Yes	High
McCarthy et al.	Yes	Yes	No	No	No	Yes	Intermediate
Horino et al.	Yes	Yes	No	Yes	No	Yes	High
Pal et al.	Yes	Yes	No	Yes	No	Yes	High
Agarwal et al.	Yes	Yes	No	Yes	No	Yes	High
Labanaris et al.	Yes	Yes	No	Yes	No	Yes	High
Mardani et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Basiri et al.	Yes	Yes	No	Yes	No	Yes	High
Duenas-Garcia et al.	Yes	Yes	No	Yes	No	Yes	High
Png et al.	Yes	Yes	Yes	Yes	Yes	Yes	High

Yeh et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Li et al.	Yes	No	Yes	Yes	Yes	Yes	High
Radha Krishna et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Rangarajan et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Ketata et al.	Yes	Yes	No	Yes	No	Yes	High
Dooldeniya et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Vohra et al.	Yes	Yes	No	Yes	No	Yes	High
Jurisic et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Pradhan	Yes	Yes	Yes	Yes	Yes	Yes	High
Kato et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Kaur et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Hwang et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Puri et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Stein et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Pal et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Bultitiude et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Neel	Yes	Yes	Yes	Yes	Yes	Yes	High
Wandabwa et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Lynn et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Misra et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Abuzoda et al.	Yes	Yes	No	Yes	No	Yes	High
Dangerfield et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Gogus et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Oteng-Ntim et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Tan et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Eckardt et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Jayathillake et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Basavaraj et al.	Yes	Yes	No	Yes	No	Yes	High
Jutley et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Goel et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Peeters et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Nishimura et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Ortega-Carnicer et al.	Yes	Yes	No	Yes	No	Yes	High
Webb et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Fujikawa et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Munshi et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Jorion et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Stebbing et al.	Yes	No	Yes	Yes	Yes	Yes	High
Atalay et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Pintar et al.	Yes	No	Yes	Yes	Yes	Yes	High
O'Neill et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Patel et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Tuncer et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Aanestad et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Kekre et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Lapointe et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Kumar et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Ekuma-Nkama et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Tabaru et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Addar et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Wystrychowski et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Comiter et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Roberts et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Tay et al.	Yes	Yes	Yes	Yes	Yes	Yes	High

Gimmon	Yes	Yes	Yes	Yes	Yes	Yes	High
Nishiyama et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Vandenbroek	Yes	Yes	Yes	Yes	Yes	Yes	High
Marcus et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Kibel et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Basu et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Chen et al.	Yes	No	Yes	Yes	Yes	Yes	High
Carmon et al.	Yes	No	Yes	Yes	Yes	Yes	High
Raju et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Shroff et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Itoh et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Selling Rasmusen et al.	Yes	Yes	Yes	No	Yes	Yes	High
Brown et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Hamer et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Wan et al.	Yes	No	Yes	Yes	Yes	Yes	High
Aubia et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Gough et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Lee et al.	Yes	Yes	No	Yes	No	Yes	High
Marshall et al.	Yes	Yes	No	No	No	Yes	Intermediate
Lee et al.	Yes	Yes	Yes	No	Yes	Yes	High
Newland et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Sorensen et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Lavelle	Yes	Yes	Yes	Yes	Yes	Yes	High
Hemal	Yes	Yes	Yes	Yes	Yes	Yes	High
Jee et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Keeler et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Watson et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Zerin et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Hansen et al.	Yes	Yes	No	Yes	No	Yes	High
Wujanto et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Budd	Yes	Yes	Yes	No	Yes	Yes	High
Ruston et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Haddad et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Danso	Yes	Yes	Yes	Yes	Yes	Yes	High
Ratliff et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Ramcharan et al.	Yes	Yes	No	Yes	No	Yes	High
Schein et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Shaked et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Piser et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Christensen et al.	Yes	Yes	No	Yes	No	Yes	High
Woo et al.	Yes	Yes	No	Yes	No	Yes	High
Juul et al.	Yes	No	Yes	Yes	Yes	Yes	High
Huffman et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Powell et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Kumar et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Davis et al.	Yes	No	Yes	No	Yes	Yes	High
Jenkinson	Yes	Yes	Yes	Yes	Yes	Yes	High
Shumaker et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Elem	Yes	Yes	Yes	Yes	Yes	Yes	High
Bennett et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Cumes et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Ihekwaba	Yes	No	Yes	Yes	Yes	Yes	High
Singh et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Sinha et al.	Yes	Yes	Yes	Yes	Yes	Yes	High

Karamooz et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Harding et al.	Yes	Yes	No	No	No	Yes	Intermediate
Elem	Yes	Yes	Yes	Yes	Yes	Yes	High
Agapitidis et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Maddocks et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Jackaman et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Smith et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Evans et al.	Yes	No	No	No	No	Yes	Low
Garfinkle et al.	Yes	No	Yes	Yes	Yes	Yes	High
Ashraf et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Maxwell et al.	Yes	No	Yes	Yes	Yes	Yes	High
Wheeler	Yes	No	No	Yes	No	Yes	Intermediate
Mitchell et al.	Yes	No	Yes	No	Yes	Yes	High
Kamat et al.	Yes	Yes	No	Yes	No	Yes	High
Daines et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Doig	Yes	Yes	Yes	Yes	Yes	Yes	High
Altman et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Baker	Yes	No	Yes	Yes	Yes	Yes	High
Bliss et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Hammar	Yes	Yes	Yes	Yes	Yes	Yes	High
Heffernan	Yes	Yes	No	Yes	No	Yes	High
Bastable et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Yarwood	Yes	No	Yes	Yes	Yes	Yes	High
Thomas	Yes	Yes	Yes	Yes	Yes	Yes	High
Clinton-Thomas et al.	Yes	No	Yes	No	Yes	Yes	High
Macalister et al.	Yes	No	Yes	Yes	Yes	Yes	High
Hershman et al.	Yes	No	Yes	No	Yes	Yes	High
Tainsh	Yes	Yes	Yes	Yes	Yes	Yes	High
Nemser et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Crastnopol et al.	Yes	No	Yes	Yes	Yes	Yes	High
Escue	Yes	Yes	Yes	Yes	Yes	Yes	High
Taylor	Yes	Yes	Yes	Yes	Yes	Yes	High
Oppenheimer et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Petkovic et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Feigal et al.	Yes	Yes	Yes	No	Yes	Yes	High
Nobel	Yes	No	Yes	Yes	Yes	Yes	High
Marbury et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Lipow et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Wyatt et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Morton	Yes	Yes	Yes	Yes	Yes	No	High
Dixon et al.	Yes	No	Yes	No	Yes	Yes	High
Saphir et al.	Yes	Yes	Yes	Yes	Yes	Yes	High
Cave	Yes	Yes	Yes	Yes	Yes	Yes	High
Stone	Yes	Yes	No	No	No	Yes	Intermediate
Alton	Yes	Yes	Yes	No	Yes	Yes	High
Sisk	Yes	No	No	No	No	Yes	Low
White	Yes	Yes	Yes	Yes	Yes	Yes	High

Questions - comprise the tool for assessing the methodological quality of each of the included articles:

1. Does/do the patients represents the whole experience of the investigator or is the selection method unclear to the extent that other patients with similar presentation may not have been reported?
2. Was the condition adequately ascertained?
3. Was the outcome adequately ascertained?
4. Were other alternative causes that may explain the observation ruled out?

5. Was follow-up long enough for outcomes to occur?
6. Is/are the cases described with sufficient details to allow other investigators to replicate the research or to allow practitioners to make inferences related to their own practice?
*High quality: "yes" answer to four or more questions, intermediate quality: "yes" answer to three questions, low quality: "yes" answer to less than three questions.

Supplementary Table 2: Clinical presentation of patients diagnosed with SRUB

	n (%)
Presenting symptoms (n=351)	
No symptoms specified	10 (2.8)
Abdominal distention	74 (21)
Abdominal pain	267 (76)
Unspecified abdominal pain	128 (36)
Generalised abdominal pain	39 (11)
Localised abdominal pain	100 (28)
Lower abdomen	79 (23)
Suprapubic	9 (2.6)
Epigastric	5 (1.4)
Right iliac fossa	2 (0.6)
Periumbilical	2 (0.6)
Back	2 (0.6)
Right upper quadrant	1 (0.3)
Urinary symptoms	259 (74)
Anuria	33 (9.4)
Oliguria	57 (16)
Dysuria	28 (8.0)
Haematuria	57 (16)
Urgency/frequency	19 (5.4)
Acute urinary retention/difficulty voiding	63 (18)
Unspecified urinary symptoms	2 (0.6)
Fever/rigors/chills	25 (7.1)
Nausea and/or vomiting	79 (23)
Anorexia	10 (2.8)
Fatigue/malaise/generalised weakness/lethargy	4 (1.1)
Pedal oedema	2 (0.6)
PV bleeding	1 (0.3)
Constipation/obstipation	10 (2.8)
Diarrhoea	10 (2.8)
Confusion	5 (1.4)
Dyspnoea	7 (2.0)
Discolouration abdominal wall	1 (0.3)
Examination findings (n=351)	
No findings specified	47 (13)
Abdominal distention	131 (37)
Abdominal tenderness	84 (24)
Unspecified abdominal tenderness	24 (6.8)
Generalised tenderness	6 (1.7)
Localised tenderness	10 (2.8)
Suprapubic	5 (1.4)
Right iliac fossa	2 (0.6)
Lower abdomen	3 (0.9)
Generalised peritonitis	34 (9.7)
Localised peritonitis	12 (3.4)

Unspecified site	6 (1.7)
Suprapubic	5 (1.4)
Hypogastrium	1 (0.3)
Ascites	45 (13)
Hypotension	14 (4.0)
Tachycardia	2 (0.6)
Tachypnoea	1 (0.3)
Respiratory distress	3 (0.9)
Confusion	10 (2.8)
Pyrexia	34 (9.7)
Hypothermia	1 (0.3)
Decreased bowel sounds	15 (4.3)
Absent bowel sounds	14 (4.0)
Abdominal mass	9 (2.6)
Pedal oedema	1 (0.3)
Scrotal and penile oedema	1 (0.3)
Pelvic organ prolapse	2 (0.6)
Vaginal bleeding	1 (0.3)
Peritoneo-cutaneous fistula	1 (0.3)
Haematuria	3 (0.9)
Anuria	1 (0.3)
Discolouration abdominal wall	1 (0.3)
Normal abdominal examination	1 (0.3)

RESEARCH PROTOCOL

Spontaneous Bladder Rupture: Demystifying the Condition – A Systematic Review

Research protocol in partial fulfilment for the degree of Master of Medicine in Emergency Medicine

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INTRODUCTION AND BACKGROUND

Rupture of the urinary bladder is a life-threatening urological emergency. It requires prompt diagnosis to prevent significant morbidity and mortality. The vast majority of cases of bladder rupture is secondary to injury but, in 3.4% of cases, there is no prior history of trauma (1). The diagnosis becomes considerably more challenging, placing this particular subset of patients at considerable risk due to the time delay to definitive management. Much of the aetiology and risk factors associated with this condition appear to be poorly understood.

Spontaneous rupture of the urinary bladder (SRUB) is defined as perforation or rupture of the bladder into the peritoneal cavity or extra-peritoneal rupture, in the absence of trauma or direct stimulation (2,3). This term also excludes cases where the rupture has occurred as a direct result or complication of instrumentation or previous bladder surgery, e.g., cystoscopy or transurethral resection of bladder tumour (TURBT).

Spontaneous rupture of the urinary bladder appears to be a relatively rare condition. The incidence has previously been described in the literature as 1:126 000. This was determined by Bastable et al. in 1959, who compiled a series of cases over 25 years (4,5). Later studies have shown that the actual incidence may be as high as 1:50 000 (6).

Despite the relatively low reported incidence of SRUB, the mortality rate appears to be

significant, ranging from 47% to as high as 80% (5,7). It seems that the risk of mortality may be somewhat related to the underlying undiagnosed condition associated with the rupture of the bladder (8). There has been little described as to the actual cause of death in many of these patients.

The presentation of SRUB is not unique. Patients tend to present to the ED with severe, acute onset abdominal pain as the chief complaint (9,10). This is normally associated with several other symptoms, including anuria, oliguria, haematuria, fever, and rigors (6). The major clinical findings are abdominal tenderness and ascites. Abdominal pain is a common presenting complaint in the ED across all demographics, and the acute abdomen carries a long list of differential diagnoses. This makes evaluation of these patients particularly difficult as the presentation is similar to many other life-threatening conditions.

Due to the peritoneal reabsorption (described as reverse auto-dialysis) of urea and creatinine, patients often present with laboratory findings indicative of severe acute kidney injury (AKI). One case series found the rate of AKI as high as 80% (6). It must be noted that this is not necessarily a true renal failure and actual kidney function is initially normal in these patients (11–13). This does not mean that early supportive care is not necessary. High levels of urea have similar effects as in actual renal failure, and this can add to the already confusing clinical picture if this is not considered early on. In addition, due to the same mechanism, there are often multiple electrolyte abnormalities which can be life-threatening if not managed promptly.

Due to the spontaneous onset of this condition and the generally low index of suspicion, there is often a prolonged time to diagnosis and a high rate of misdiagnosis. One case series determined a misdiagnosis rate of 66.7% in their centre (6). The challenge associated with an accurate and timeous diagnosis is not difficult to understand. The main confounding variable appears to be as a result of the effects of urinary ascites and peritoneal reabsorption of urine leading to prolonged uraemia and electrolyte disturbances, which can result in cardiac arrest, intra-abdominal sepsis and septic shock, bowel necrosis resulting in obstruction, hollow viscus perforation, and ultimately death (14-16). Due to multiple factors confounding the ability to diagnose SRUB accurately in patients presenting with abdominal pain, the emergency physician's high index of suspicion remains key.

Patients presenting with acute abdominal pain often require urgent imaging to discern the cause. Ultrasound is a useful modality for ruling out other potential causes, but due to its relatively low specificity, it has a limited role in the actual diagnosis of bladder rupture (17).

As previously discussed, patients often present with abnormal kidney function on laboratory investigations. This makes the use of potentially nephrotoxic contrast for imaging a point of contention. A computed tomography study of the abdomen and pelvis with retrograde cystography (CT-RC) is considered the investigation of choice, with a specificity of 95.9% compared to CT without cystography (including delayed-phase) with a specificity of 60.6% (18). In the ED setting, this investigation in frequently requested in the setting of trauma but seldom considered in patients presenting with spontaneous bladder rupture. Despite the high sensitivity of CT-RC, the accuracy is still user-dependent and hinges mainly on the following of standard protocols. CT-RC has the distinct advantage of imaging the entire abdomen and pelvis to exclude other potential causes or complications. Static fluoroscopic plain-film retrograde cystography also has a high specificity (85-100%), but its use is often hampered by resource constraints related to personnel and equipment (17).

Despite the number of diagnostic modalities at the clinician's disposal, often the diagnosis is only made intraoperatively. Patients presenting to the ED with an acute abdomen are emergently taken to theatre, and the diagnosis is made either by cystoscopy, laparoscopy, laparotomy, or a combination of these methods.

The use of point-of-care ultrasound has become an essential tool in the assessment of patients with abdominal pain in the ED. The experienced user can gain immediate insight into possible life-threatening causes of abdominal pain. This includes gallbladder disease, abdominal aortic aneurysm, urolithiasis, intraabdominal infections, and the presence of free fluid, amongst others. Bedside ultrasound in the ED has been used to assess for potential bladder rupture in those patients with a history of trauma (19). This use has been extended to those patients without a history of trauma in several studies (20,21). Typical findings include: the presence of free fluid, a collapsed bladder with minimal output during urinary catheterisation, visualisation of the catheter bulb outside the bladder, the presence of turbulent fluid motion outside of the bladder with saline irrigation through the urinary catheter and in some cases, a defect of the bladder wall may even be visualised (21).

Spontaneous rupture of the urinary bladder has been reported in the literature for over 100 years. Case reports date back to as early as 1916 when White and Wigram first described it in the British Journal of Surgery as a rare and obscure condition (22). This particular case was a patient with a neurogenic bladder and chronic cystitis that eventually resulted in a spontaneous perforation. The majority of evidence on this condition consists of case reports or small case series. A handful of studies have carried out literature reviews in addition to reporting on their own cases (8,9,17,23,24). Although case reports and case series are generally regarded as lower levels of evidence in the hierarchy of medical literature, they have a big role to play in reporting on patient characteristics and predisposing factors of rare conditions.

Several case series have attempted to report on the potential causative or underlying risk factors predisposing patients to SRUB. The underlying pathophysiology is generally regarded as being a combination of reduced bladder wall integrity (either structural or due to over-distention as a result of obstruction) and increased intra-abdominal pressure (25). On initial search of the literature, there appear to be several potential predisposing factors **(Table 1)**.

Table 1: Major groups of conditions associated with SRUB

Category	**Examples**
Drug or alcohol-related	Alcohol intoxication, pharmacological drugs (neuroleptics, opioids)
Undiagnosed bladder malignancy	Transitional or squamous cell carcinoma
Post pelvic irradiation	Radiation for known pelvic malignancy, e.g., cervical, ovarian, uterine, endometrial, prostate
Inflammation	Eosinophilic or interstitial cystitis, ulceration secondary to undiagnosed vesicolith
Infection	Bacterial, fungal, or parasitic cystitis
Physical bladder outlet obstruction	Undiagnosed congenital abnormalities (e.g., posterior urethral valves), urethral strictures, external compression (e.g., colorectal lesions, faecal loading, uterine compression from obstructed or difficult labour)
Obstruction due to bladder dysfunction (neurogenic bladder)	Post-stroke, spinal cord pathology (tabes dorsalis, myelitis, etc.)

Despite a significant number of case reports and case series published on this condition, there appears to be no systematic reviews carried out to date. The evidence has not previously been appraised and compiled to determine the underlying associations and clinical characteristics of patients diagnosed with SRUB. In addition, the descriptive nature of the case report means that there is considerable variation between studies. Each author has a different idea of what is important enough to be included and what should be omitted. This amount of heterogeneity

between studies can be challenging when attempting to carry out a systematic review. However, there are several tools available that can be used to appraise the content of a case report or case series in an objective manner. A well-described tool is the tool proposed by Murad et al. for case reports and case series. This tool was developed and proposed in 2018 and provides a structured approach to critically appraise case reports and case series (26). This checklist can help decide whether a particular study is complete and transparent enough to be included in a more extensive review that may inform future clinical study design and practice.

Systematic reviews of case reports and series have been used in the past to gather information and data to increase knowledge and awareness of rare conditions. It has been shown numerous times that this is an important but often overlooked contribution to the understanding of conditions that present sporadically (27). It is often the only form of evidence reporting on rare disorders.

Therefore, this study aims to conduct a systematic review of the literature to determine the demographics, clinical characteristics, diagnostic modalities, morbidity, and mortality of patients diagnosed with SRUB in order to determine if there are predictive factors present to reduce the time to diagnosis and definitive management, with the ultimate goal of improving patient outcomes.

STUDY OBJECTIVES

- To conduct a systematic review in keeping with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement guidelines of studies relating to SRUB
- To determine if there are any predictive factors present that can aid in the diagnosis of this condition by describing the demographics of patients diagnosed with SRUB
- Identifying and describe possible predisposing factors leading to increased risk of SRUB e.g., co-morbidities, recent drug or alcohol use
- To describe the clinical characteristics of patients diagnosed with SRUB

METHODS

Study design

Systematic review

Search strategy

The following electronic databases will be searched: PubMed, Scopus, Web of Science, The Cochrane Database of Systematic Reviews, EMBASE, and Google Scholar. The search terms: 'urinary bladder' AND 'rupture' AND 'spontaneous' will be used. The following inclusion criteria will be applied as limits during each search: studies related only to the human species and studies published in the English language.

Studies will be pooled. A backward citation search will be carried out to identify studies that were missed during the original search. A reference manager will be used to collect studies and eliminate duplicates.

Study selection

Once duplicate studies have been removed from the pool, titles and abstracts will be scrutinised, and the below criteria applied to screen for ineligible studies.

Exclusion criteria:

- Studies that were found as a result of keyword matching or tags but were obviously irrelevant to the study topic
- Any preceding history of trauma
- Any known structural bladder abnormality or known bladder lesion, e.g., Bladder malignancy or exstrophy
- Cases in which bladder rupture has occurred as either a complication of a surgical procedure or as a complication of a known condition, e.g., Tubo-ovarian complex or appendicitis
- Any recent history of instrumentation or bladder surgery that can be directly linked to the rupture, e.g., augmentation, cystoscopy, neobladder, partial cystectomy, bladder stone removal, transurethral resection of bladder tumour
- Intrapartum bladder rupture as a result of traumatic vaginal delivery or as an iatrogenic complication during Caesarian section
- Bladder rupture diagnosed in the ante-natal period or presenting during the neonatal period
- Unable to locate the full-text article

Every attempt will be made to locate full-text articles, including contacting corresponding authors where possible. The final search strategy will be represented in a flow diagram in accordance with the PRISMA statement.

Risk of bias

The tool proposed by Murad et al., will be used to decide whether eligible studies are complete enough to be included in the final review. Studies will be independently rated by two researchers (DR and AL) and if any disagreement exists, a third researcher (AA) will make the final decision.

Data extraction

Data will be extracted from the pool of eligible studies using the full-text articles. Data will be collated using Microsoft Excel. The following categories of data will be collected: study details, number of patients and patient demographics, clinical characteristics of patients, diagnosis and patient outcomes. The full list of data variables to be extracted is included in the appendix.

Review format

This systematic review will be carried out in accordance with the PRISMA statement. The PRISMA statement provides a comprehensive framework of components that should be included in a systematic review to ensure transparency and reproducibility (28).

DATA ANALYSIS

Univariate descriptive data will be calculated for each of the following variables: age (years), time to presentation (hours), time to diagnosis (hours), laboratory findings, i.e., urea and creatinine (mmol/l and μmol/l respectively). If data is parametric and normally distributed, then the mean and standard deviation will be calculated; if data is either parametric and not normally distributed or non-parametric, then the median and range will be calculated. The remainder of the data is categorical descriptive data, and percentages and ratios will be calculated for these variables: gender, clinical characteristics, associated factors, and diagnostic-related data.

ETHICS

As this study will be a retrospective review of documents already in the public domain, an

application for waiver of ethics clearance will be submitted to the University of Witwatersrand Human Research Ethics Committee (medical). There will be no active human participation in this study.

TIMING

	2021			2022										
	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov
Literature review														
Preparing protocol														
Protocol assessment														
Ethics application														
Collecting data														
Data analysis														
Writing up paper/research														

FUNDING

The researcher will cover all expenses related to the study. This will include the cost of printing and data for internet usage. There are no further foreseen costs, and this amount should total approximately R500.

PROBLEMS

As the basis for any systematic review is existing literature, the quality and availability of relevant documents will present the biggest challenge. Case reports were not previously appraised to the same degree as other forms of studies, so data can be inconsistent and incomplete in some cases. If certain sought-after data is not included in the report, it can lead to difficulty in incorporating the study in the review. Similarly, as with all descriptive studies, it is often left to the author to draw conclusions about possible associations and make inferences based on their personal experience, leading to a certain level of bias in some cases. Using a checklist to appraise studies can help reduce the impact of this potential limitation and offer some standardisation.

Despite best efforts, there may ultimately be several studies where the full text cannot be located, particularly for older publication dates. These studies will then have to be excluded from the review.

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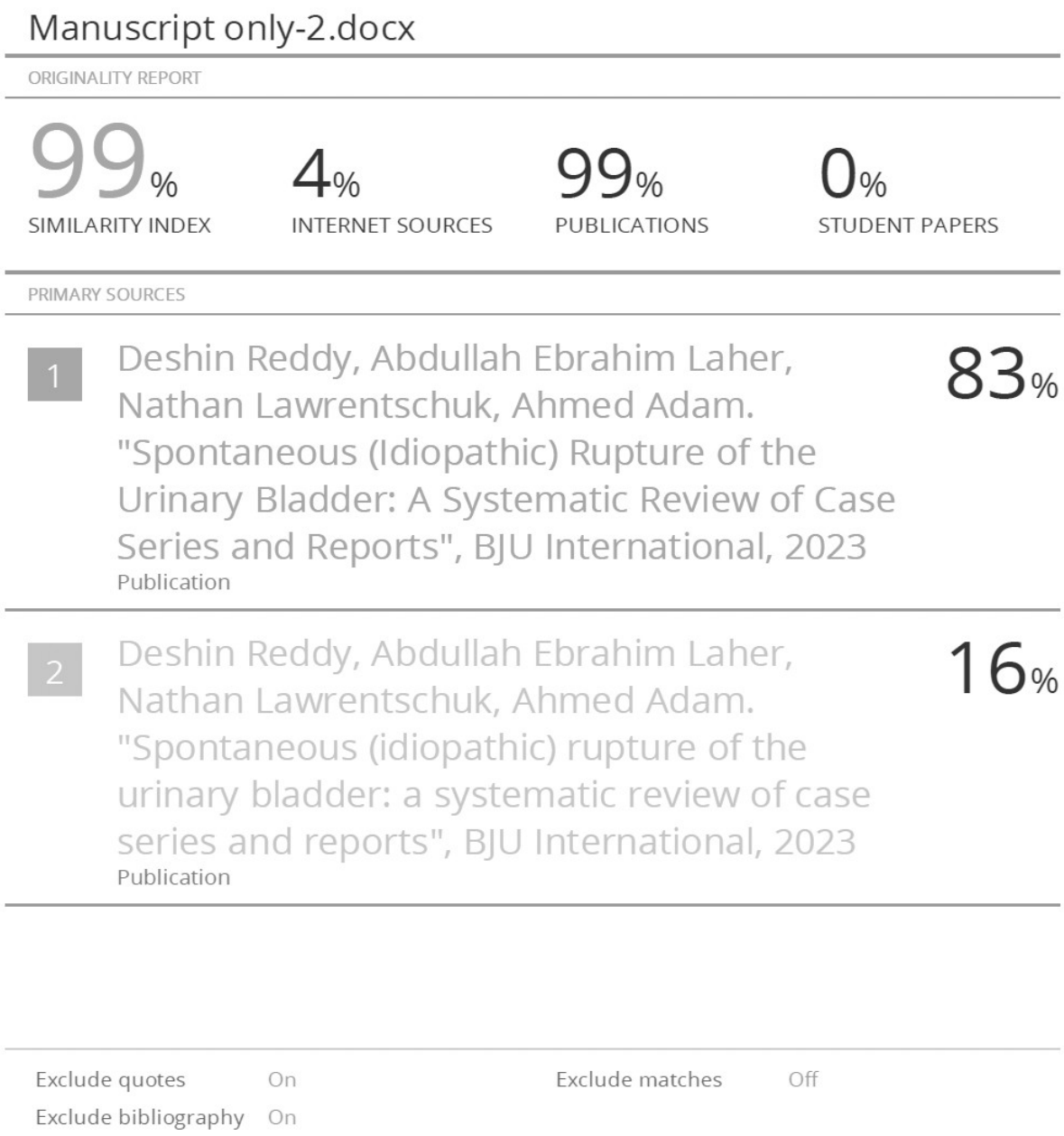
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