World Journal of Urology (2019) 37:759–776
https://doi.org/10.1007/s00345-018-2424-2

REVIEW

Mortality from kidney stone disease (KSD) as reported in the literature over the last two decades: a systematic review

Lily Whitehurst[1] · Patrick Jones[2] · Bhaskar K. Somani[2]

Received: 15 March 2018 / Accepted: 25 July 2018 / Published online: 27 August 2018

Abstract

Introduction Current trends show a rising incidence of kidney stone disease (KSD) globally, with a lifetime risk of 10% and increasing hospital admissions. However, it is not perceived as a life-threatening condition and there are no publications examining its mortality rate. The aim of this review was to report on the number of KSD mortalities in the literature from the past two decades, identify risk factors, and to summarize their key learning points.

Methods A search was conducted for full-text English language articles that reported on KSD associated mortality, following intervention or conservative treatment, published between 1999 and 2017, using PubMed, MEDLINE, EMBASE, Scopus, CINAHL, Clinicaltrials.gov, Google Scholar and The Cochrane Library. Study quality and risk of bias assessment was undertaken using a validated critical appraisal tool from the Joanna Briggs Institute.

Results Of the 2786 articles identified, 34 were included. Of the total number of reported mortalities (2550), 21% were related to intervention. Sepsis was the leading cause of mortality. Risk factors identified were patients with multiple co-morbidities, spinal cord injury or neurogenic bladder and high stone burden. The main recommendations suggested were to treat pre-operative UTI or use prophylactic antibiotics and to reduce operative duration. The included studies were of moderate to good quality.

Conclusion Pre-procedural optimization of the patients is the key to avoiding KSD mortality, and care should be taken in patients with multiple co-morbidities. Surgeons should meticulously plan for patients with high stone burden to reduce their operative time, as mortality can be procedural related.

Keywords Mortality · Ureteroscopy · Lithotripsy · SWL · Stone · Percutaneous nephrolithotomy · PCNL · Urolithiasis

Introduction

Current trends show a rising incidence of kidney stone disease (KSD) globally, with an overall lifetime risk of 10% [1–3]. It has been to be shown as a highly prevalent disease; with rates from 7 to 13% in North America, 5–9% in Europe and 1–5% in Asia [2]. Patients are more frequently presenting with sepsis as a result of infected urolithiasis [4], and with rising patient numbers, there has been a resultant increase in demand on healthcare service providers, with increase in both elective and emergency admissions [3]. Together, these trends are reflected in the exponentially increasing costs of KSD worldwide, and in the United States alone, expenditure is reported to exceed $5 billion per year [1].

As to be expected, intervention rates for KSD are also on the incline. Ureteroscopy (URS) has been shown to have increased significantly in global trends over the past two decades, whereas for other techniques such as shockwave lithotripsy (SWL) and percutaneous nephrolithotomy (PCNL), the rates have remained more static [5, 6]. Alternatively, KSD can also be managed more conservatively with an 'active surveillance' approach. Overall, KSD is not perceived as a life-threatening condition. In the literature, many authors report on complications of KSD, and each of

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00345-018-2424-2) contains supplementary material, which is available to authorized users.

✉ Lily Whitehurst
lilyalicewhitehurst@doctors.org.uk

[1] Department of Urology, Queen Alexandra Hospital, Southwick Hill Road, Cosham, Portsmouth PO6 3LY, UK

[2] Department of Urology, University Hospital Southampton NHS Foundation Trust, Tremona Road, Southampton SO16 6YD, UK

the various treatment modalities, but there has been no collation of the data on mortality.

The aim of this review was to ascertain the number of mortalities from KSD reported in the literature over the past two decades, identify relevant patient risk factors, and to summarize the key recommendations so that lessons can be learnt, and similar instances can be avoided.

Methods

A systematic literature search was conducted, following Cochrane and preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines, through PubMed, MEDLINE, EMBASE, Scopus, CINAHL, Clinicaltrials.gov, Google Scholar and the Cochrane Library for full-text English language articles published between, and reporting on data from 1999 to October 2017. Medical subject headings (MeSH) terms used, but not limited to, were: 'urolithiasis', 'kidney stone', 'renal stone', 'urinary calculi', 'urinary stone', 'renal calculi', 'percutaneous nephrolithotomy', 'shockwave lithotripsy', 'ureteroscopy', 'active surveillance', 'conservative', 'mortality', 'life-threatening' and 'death'. Boolean operators (AND, OR) were used to refine the search. The full search matrix used is included in Appendix 1.

Inclusion criteria

- All English language articles.
- Articles reporting on adult patients.
- Data from the last two decades only.
- All articles which reported on mortality from KSD and the relevant interventions' mortality rates.

Exclusion criteria

- Animal studies.
- Case reports.
- Articles published using the same data under a different title or author.

Though single case reports and systematic reviews were not included, their references were examined to avoid missing a relevant study for inclusion. The search process and the data extraction were undertaken by two authors (L.W., P.J.) independently and any discrepancy was clarified and sorted after arbitration by the senior author (B.K.S.). Where additional information or clarification was needed, the primary authors of the studies were contacted directly.

The PICO statement for this review is as follows: the population examined was patients of all ages who died of KSD or its related interventions. The related interventions were URS, PCNL, SWL, open surgery or conservative treatment. There was no comparative group, and the outcomes were to ascertain the number of mortalities from KSD reported in the current literature, identify which patients are more at risk of complications and to summarize the learning points so mortality can be reduced in the future.

Results

Our search produced 2786 articles, of which 34 met our inclusion criteria and were then included in our analysis. Full details of this search are depicted in the PRISMA diagram in Fig. 1. The following variables were collated from each study: year of publication, country of origin, study period encompassed, intervention type, number of mortalities, reason for mortality, important clinical parameters, learning points and recommendations. Study quality and risk of bias assessment were undertaken using a validated critical appraisal tool from the Joanna Briggs Institute (JBI) [7].

Overall mortality

The total reported number of mortalities in the current literature was 2550, which is shown in Table 1a. This comprised of all intervention types, including conservative treatment. Unfortunately, the included articles did not all state the total number of patients included in each of their studies, and thus we cannot calculate the percentage of the number of mortalities that this represents. The category included as 'multiple interventions' includes the studies [8–11] which do not specifically detail which treatment arm resulted in the mortality. Consequently, it includes PCNL, URS, SWL and conservative management and thus it is the largest category comprising 78% of the total mortalities. Notably of these studies, Kum et al. [9] included data from the Office of National Statistics over a 15-year period (1999–2013) in England and Wales. The authors included all patients with a diagnosis of urolithiasis according to the International Classification of Diseases (ICD)-10 classification, which totalled 1954 deaths. However, they provided no detail into the individual's stone or the general management of these patients. Though Kum et al. [9] has been included for the overall number of KSD mortality in the literature, it has been listed as 'non-specified stone mortality', or even excluded, in consequent tables to clarify this difference.

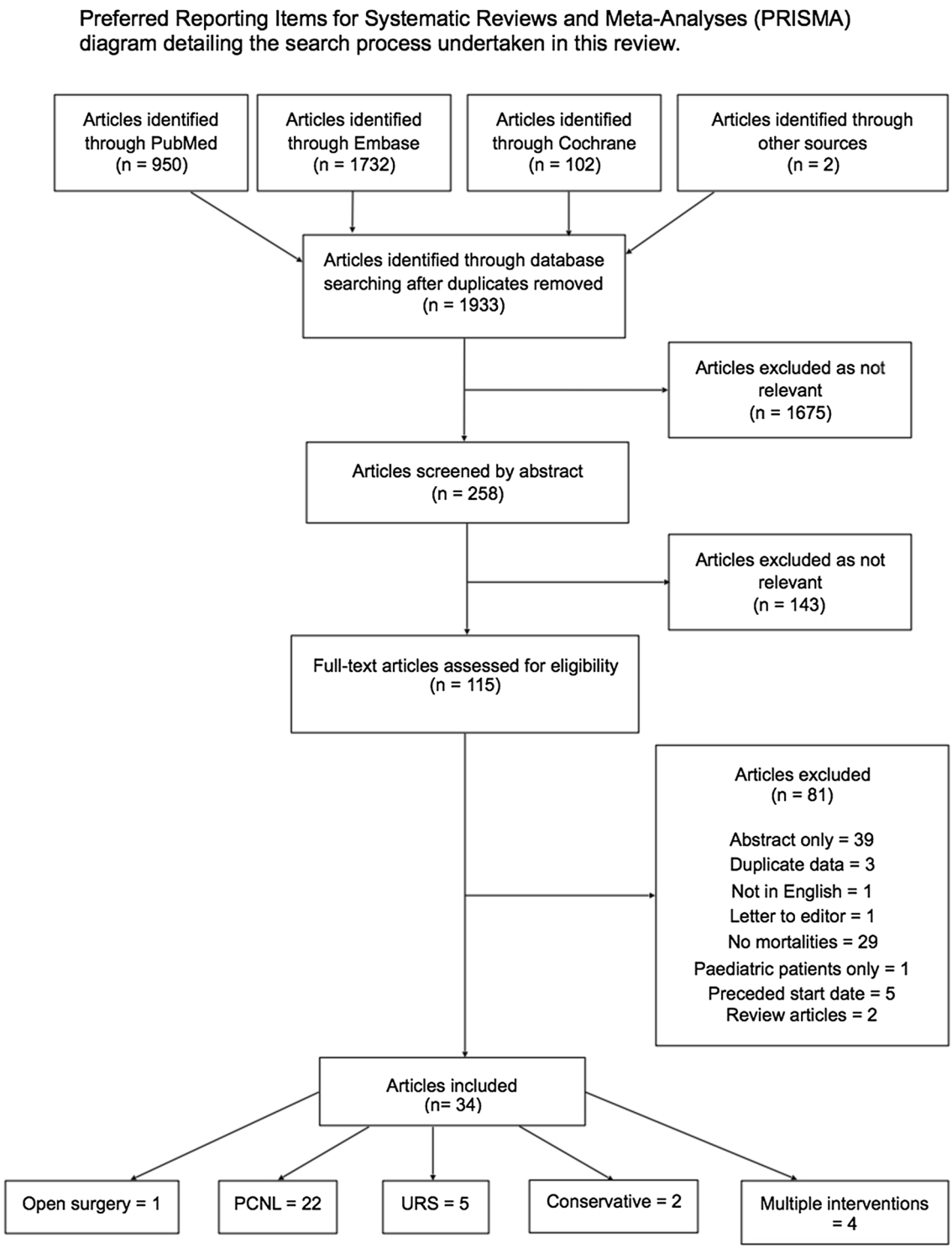

Fig. 1 Preferred report items for systematic reviews and meta-analysis (PRISMA) diagram detailing the search process undertaken in this review

Number of mortalities from intervention

As previously mentioned, there were few studies that include data on multiple interventions, which have been classified separately. The articles which focussed on a sole intervention; such as PCNL, URS, or open surgery, showed a related mortality of 530 patients, which accounted for 21% of the overall total. If the 'non-specified stone

Table 1 Overall mortality of KSD reported in the literature in the last two decades, and intervention-related mortality of KSD

(a)

Intervention type	Number of studies	Number of mortalities (% of total)	Percentage of total mortalities (%)
PCNL	22	507	19.9
URS	5	21	0.8
Conservative	2	30	1.2
Open surgery	1	2	0.1
Multiple interventions and other non-specified stone mortality*	4	1990 (*1954)	78.0
Total	34	2550	

(b)

Intervention			Cause of death							
Intervention type	Number of studies	Number of mortalities	Sepsis	Haemorrhage	Respiratory complication	Multi-organ failure	Cardiac complication	Colonic injury	Not specified	Overall mortality (%)
PCNL	22	507	18	10	4	3	2	1	469	85.3
URS	5	21	6	1	2	1	3	0	8	3.5
Open surgery	1	2	1	1	0	0	0	0	0	0.2
Total	28	530	25	12	6	4	5	1	477	89.0
Conservative	2	30	0	0	0	0	0	0	30	5.0
Intervention and conservative (not including Kurn et al.)	3	36	29	0	0	1	0	0	6	6.0
Total	33	596	54	12	6	5	5	1	513	

Table 2 Significant risk factors contributing to KSD mortality

Risk factor identified	Number of articles which deem the risk significant	Number of mortalities related to this risk
High number of patient co-morbidities	7	369
Spinal cord injury patients	2	145
High stone burden patients	4	9
Neurogenic bladder patients	3	8
Obesity	2	5

mortality' from Kum et al. [9] is excluded, then intervention related mortality accounted for 89%. Table 1b also displays intervention-related mortality, with majority of the included studies (65%) reporting on PCNL. The number of PCNL related deaths was 85.3% of the total, thus the most common intervention related mortality. Open surgery was accountable for 0.2% mortality; however, only one included study reported on this [39].

Number of mortalities from conservative treatment

Only 2 [40, 41] of the 34 articles reported on conservative management-related mortality, and there were 30 reported deaths. There was some cross-over by the article Hussain et al. [8], which is included in 'intervention and conservative' category in Table 1b. In their study, patients were split into those initially treated with conservative measures or those who received definitive treatment. However, the number of mortalities specifically caused by conservative

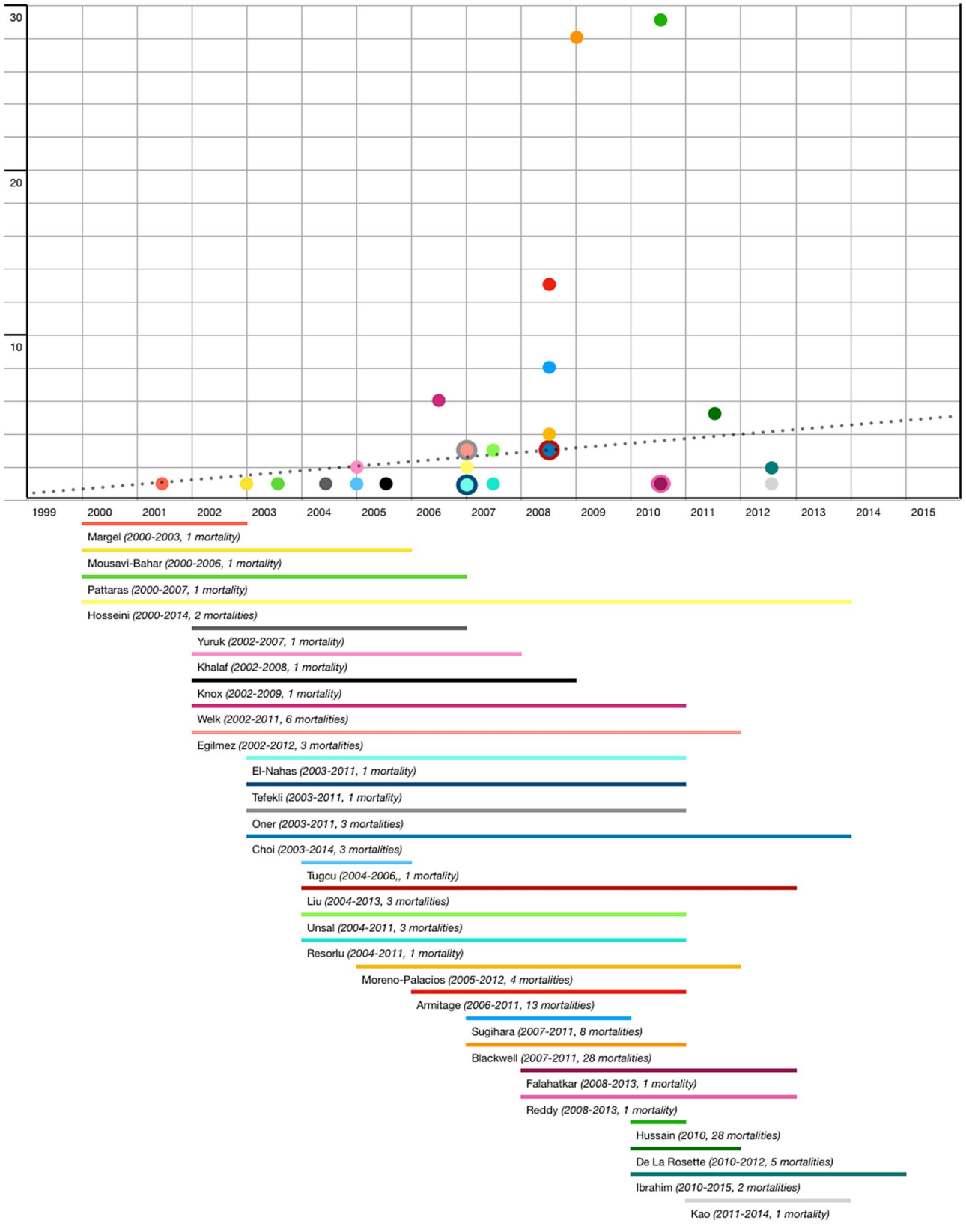

Fig. 2 Trends of KSD mortality over the past two decades

management is not stated, thus the necessity to classify it separately.

Reason for mortality

All of the recurrent mortality causes are displayed in Table 1b, and this clearly demonstrates that sepsis was the most common cause, representing 9%. Haemorrhage was shown to be the second most significant cause, comprising 2% of the mortality-related complications. Unfortunately, over 85% of the included studies did not explicably state the mortality cause, thus these data are limited.

Significant clinical risk factors

The recurring, significant risk factors reported in the literature are shown in Table 2. The number of mortalities attributable to each of these individual risk factors is also included. The most pronounced risk factors for mortality were patients with high numbers of co-morbidities, as authors stated that for 369 patients, this was found to increase their risk of complication, and thus mortality. The other common themes were: patients with spinal cord injury, neurogenic bladder or those with a high stone burden, and obese patients. In addition to Kum et al. [9], seven other articles did not identify any significant risk factors. The article by Hussain et al. [8], must be mentioned, as although it reported on 29 fatalities, the study comprised patients predominantly from rural Pakistan (72.3%) and of low socioeconomic class (77.6%) whose presenting complaint to the tertiary centre was renal failure. Thus, the overall conclusions were that their high mortality rate was due to the patients' late presentation and this can potentially be tackled by increasing public awareness of KSD in Pakistan, as this was a solitary article it has not been included in the table as a significant risk factor.

Trends over time

Figure 2 shows a chronological representation of the mortality trends, and the relevant articles split into the time trends for each intervention are shown in Table 3. The articles by Kum et al. [9], Ghani et al. [12] and Baldea et al. [13] were excluded from the graph, as all of these studies used national databases of the UK and USA to source their mortality numbers. They all individually reported > 100 mortalities which was exceptionally high in comparison to other studies. Of the included articles, the data period encompassed by each study was used to build the picture of chronology, with the mid-point being used to represent the mortality number. The overall trend showed that there has been an increasing rate of mortality over the past two decades.

Geographical significance

The country and continent of each included study were analysed, and the data are shown in Table 4. It is shown that the majority of included studies were from Asia. Fifteen of these Asian studies were related to PCNL, with Turkey featuring in seven of these studies reporting on 14 of the total deaths. Not including the National database study from Kum et al. [9, 15] 15% mortality was reported from Europe. Similarly, excluding the National database study from Ghani et al. [12] and Baldea et al. [13, 20] 20% mortality was reported from North America. The clinical research office of the Endourological Society (CROES) database on URS contributed to five deaths although this was 0.04% of the total number of procedures reported [15]. As this was worldwide data contributed and reported by individual urologists, we have categorized it separately as 'global'.

Key messages for avoidance

Most of the studies made key recommendations for the urological audience as how to avoid complications resultant of KSD. These findings are summarized in Table 5, with a breakdown specific to each intervention type as a takeaway message. The main recommendations from all studies were to treat pre-operative UTI, use prophylactic antibiotics, reduce operative duration, ensure diligent hemostasis and remain cautious in patients with a high stone burden. The recommendations were made by authors to reduce morbidity from KSD; however, as the included articles all included mortality figures, these have been adopted as by consequence also reduce KSD mortality.

Risk of bias assessment

The JBI tool [7] was used to award each study with a score from 1 to 10. Scores of 1–5 were deemed as poor–moderate, and scores of 6–10 were deemed as moderate–good. Of the included articles, 3/34 were deemed poor–moderate, and 31/34 were moderate–good which is shown in supplementary Fig. 2. As the majority of the included papers fell within the moderate–good category, the overall quality of the included articles was of fair quality with minimal bias.

Discussion

This is the first study to collate and summarize trends of KSD mortality across the world. Thirty-four studies were identified from the literature, which demonstrated data from over 16 countries, in the last two decades. Various treatment modalities were included such as: URS, PCNL, SWL, open

surgery and conservative management. This review identified 2550 reported deaths, and demonstrated a chronological trend of increasing KSD mortality being published in the literature. With escalating numbers of KSD-related procedures being performed, the key learning points from each study were identified. Additionally, a summary of risk factors for the prevention of future similar instances is detailed, highlighting that an individual patient-centred approach is cardinal for success.

Key findings of our study

The increasing global incidence of KSD is likely contributed to by dietary changes, a reduction in oral fluid intake, obesity, increased life expectancy and climate change [6], and though some of these factors are unavoidable, and the consequential increasing onslaught of KSD poses troublesome concerns for health services. Various treatment options exist for the management of KSD and the current European Association of Urology (EAU) guidelines recommend URS or SWL as first line treatment for kidney stones < 2 cm, and PCNL for stones > 2 cm [42, 43]. Of the 2550 mortalities recorded from our literature search, just over one-fifth (530 mortalities) were related to KSD intervention. This discrepancy is attributable to the longitudinal report from national reporting data by Kum et al. [9], which provided 1954 mortalities. The authors used (ICD)-10 code of urolithiasis to search death certificates in the UK over a 14-year time period. The figure was included for accuracy of the trends, but the article as a whole was of limited use, as it did not detail which management option led to these fatalities. This single paper contributes largely to our data, and without it the numbers are very small, thus we may consider that we may over-estimate the total number of mortalities from kidney stone disease.

URS is an emerging treatment modality due to the improving technology and advancements in the surgical technique [5], and it was only accountable for 3.5% of all mortalities. Similarly, the CROES study [15] of over 11,000 patients showed a low complication rate related to URS (7.4%) and a mortality rate of 0.04%, which supports that URS is a safe treatment option. Only one study [39] reviewed open surgery, which supports its decreasing popularity in an era of minimally invasive techniques. It contributed 0.2% of the intervention related mortalities. Contrarily, PCNL was accountable for the majority of the mortalities at 85.3%. The study by Armitage et al. [34] focussed on PCNL outcomes through mandatory reporting by individuals in the UK, and included 5780 patients. They found that haemorrhage was twice as common as sepsis (1.4 vs. 0.7%), with 5 (0.09%) and 3 (0.05%) mortalities related to haemorrhage and sepsis, respectively [34]. Very few articles included in our review specifically focussed on sepsis, although many identified that patients with UTI had a poorer outcome. Of the included articles, Liu et al. [32] set out to identify risk factors and prevent sepsis in their patient cohort undergoing mini-PCNL. They found that 2.4% of their patients developed septic shock, and 0.4% of their cohort died due to sepsis [32]. They recommended that peri-operative antibiotics should be used routinely, even in the presence of a negative urine culture [32], which is a key learning point that urologists should consider adopting. Conservative management accounted for 5% of all intervention-related mortalities. Of the conservative studies included, they all involved a specific patient cohort; for the article by Deutsch and Subramonian [41] it was patients with staghorn calculi, whereas Blackwell et al. [40] focussed predominantly on emergency admissions presenting with UTI, acute renal failure or sepsis. These specific cohorts of patients were particularly high risk, which may account for the high figure from only two studies.

The literature search included articles that encompassed countries from all over the world. According to this review, the majority of intervention related mortalities were from Asia (47.4%), and the least occurred in Africa (3.6%); however, this correlated with most of the articles included being from the Asian continent. Though this is an interesting finding, it provides little insight as to where most KSD fatalities occur, as this is only a snapshot of the number of mortalities reported in the literature and not correlated with national statistics.

One of the key aims of this review was to identify learning points for urologists and summarize risk factors that make a patient more at risk of complications from KSD interventions, and thus minimise their mortality rate. This review found that the most pronounced risk factor for mortality was patients with high numbers of co-morbidities. The other common risk factors identified were: patients with spinal cord injury, neurogenic bladder or high stone burdens, and obese patients. These were recurring themes despite the type of intervention performed. It is, therefore, paramount to have strict planning for individuals who are deemed more high risk due to their co-morbidities, or their stone burden. The recommendations made by the included authors were to reduce operative duration and plan a suitable intervention or stage their intervention, thus reducing mortality rates.

Recommendations to avoid mortality

Most of the studies made key recommendations which can be adopted by the urological audience to avoid KSD-related mortality. Though, we acknowledge that the authors' recommendations were to reduce morbidity, as all of the included datasets included mortality, we have extrapolated these recommendations to also be applicable for the reduction of KSD mortality. The findings are summarized in Table 5, with a breakdown specific to each intervention type as a

Table 3 Trends of KSD mortality over the past two decades according to intervention type

Intervention type	Number	Authors	Date period encompassed	Number of mortalities	Total number of mortalities per intervention
Intervention					
URS	1	Sugihara [14]	2007–2010	8	
	2	De La Rosette [15]	2010–2012	5	
	3	Kao [16]	2011–2014	1	
	4	Cindolo [17]	Not included	1	
	5	Cindolo2 [18]	Not included	6	21
PCNL	1	Ghani† [12]	1999–2009	320	
	2	Margel [19]	2000–2003	1	
	3	Hosseini [20]	2000–2014	2	
	4	Mousavi-Bahar [21]	2000–2006	1	
	5	Knox [22]	2002–2009	1	
	6	Yuruk [23]	2002–2007	1	
	7	Egilmez [24]	2002–2012	3	
	8	Oner [25]	2003–2011	4	
	9	El-Nahas [26]	2003–2011	1	
	10	Tefekli [27]	2003–2011	1	
	11	Unsal [28]	2004–2011	3	
	12	Choi [29]	2003–2014	3	
	13	Tugcu [30]	2004–2006	1	
	14	Resorlu [31]	2004–2011	1	
	15	Lill C [32]	2004–2013	3	
	16	Morenc-Palacios [33]	2005–2012	4	
	17	Armitage [34]	2006–2011	13	
	18	Baldea† [13]	2007–2011	139	
	19	Falahatkar[35]	2008–2013	1	
	20	Reddy [36]	2008–2013	1	
	21	Ibrahim [37]	2010–2015	2	
	22	Palnizky [38]	Not included	1	507
Open surgery	1	Khalaf [39]	2002–2008	2	2
					530
Intervention and conservative management					
	1	Kum*†[9]	1999–2013	1954	
	2	Pattaras [10]	2000–2007	1	
	3	Welk [11]	2002–2011	6	
	4	Hussain [8]	2010–2010	29	1990
Conservative management					
	1	Blaokwell [40]	2007–2011	23	
	2	Deutsch [41]	Not included	2	30
Total number of mortalities					2550

*Non-specified stone mortality

†Not included in Fig. 2

take-away message for reference. The key recommendations that can be surmised for all intervention types are as follows: reduce operative duration, aggressive treatment of preoperative UTI or the use of prophylactic antibiotics, ensure that there is diligent hemostasis throughout the procedure and caution to be taken in patients with a high stone burden. There were also specific recommendations applicable to the different types of intervention, such as in PCNL, for which the authors noted that particular care should be taken in elderly patients and endourologists should avoid forming multiple renal access tracts, as all these patients had worse outcomes comparatively. For patients who were managed conservatively, the suggestion was that any patient who presented with sepsis should undergo early decompression. The

Table 4 Geographical trends in KSD mortality

Authors	Country	Intervention type	Mortality number	Mortalities per continent
Africa				9%
El-Nahas [26]	Egypt	PCNL	1	
Ibrahim [37]	Egypt	PCNL	2	
Khalaf [39]	Egypt	Open surgery	2	5 of 2550 (0.2%) 5 of 137 (3.6%)
Asia				53%
UuG [32]	China	PCNL	3	
Choi [29]	Korea	PCNL	3	
Falahatkar [35]	Iran	PCNL	1	
Hosseini [20]	Iran	PCNL	2	
Mousavi-Bahar [21]	Iran	PCNL	1	
Margel [19]	Israel	PCNL	1	
Palnizky [38]	Israel	PCNL	1	
Reddy [35]	India	PCNL	1	
Egilmez [24]	Turkey	PCNL	3	
Oner [25]	Turkey	PCNL	4	
Resorlu [31]	Turkey	PCNL	1	
Tefekli [27]	Turkey	PCNL	1	
Tugcuan [30]	Turkey	PCNL	1	
Unsal [28]	Turkey	PCNL	3	
Yuruk [23]	Turkey	PCNL	1	
Sugihara [14]	Japan	URS	8	
Kao [16]	Taiwan	URS	1	
Hussain [8]	Pakistan	Multiple surgical interventions	29	65 of 2550 (2.5%) 65 of 137 (47.4%)
Europe				15%
Cindalo [17]	Italy/France	URS	1	
Cindolo 2 [18]	Italy	URS	6	
Armitage [34]	UK	PCNL	13	
Kurn [9]	UK	Multiple surgical interventions	1954	
Deutsch [41]	UK	Conservative	2	1976 of 2550 (77.5%) 22 of 137 (16.1%)
North America				20%
Moreno-Palacios [33]	Mexico	PCNL	4	
Baldea [13]	USA	PCNL	139	
Ghani [12]	USA	PCNL	320	
Knox [22]	USA	PCNL	1	
Blackwell [40]	USA	Conservative	28	
Pattaras [10]	USA	Multiple surgical interventions	1	
Welkn [11]	Canada	Multiple surgical interventions	6	499 of 2550 (19.6%) 40 of 137 (29.2%)
Global				3%
De La Rosette [15]	Global	URS	5	5 of 2550 (0.2%) 5 of 137 (3.6%)

article by Blackwell et al. [40] found that there was no difference in outcome for those decompressed with ureteric stents compared to nephrostomy, thus availability of an interventional radiology service does not have a negative impact on the patient's management. The recommendation from the article Kum et al. [9] that included the most mortality was the use of prophylactic antibiotic therapy to prevent urine infections, which correlated with the findings of the review

Table 5 Risk factors and key learning recommendations to reduce KSD mortality

Authors	Intervention type	Mortality number	Significant clinical parameters	Key learning point identified	Summary of key recommendations
Cindolo et al. [17]	URS	1	Neurogenic bladder patient	Avoid peri-renal haematomas during URS Treat sepsis aggressively to prevent mortality	URS: 1. Reduce operative duration 2. Aggressive treatment of pre-operative UTIs 3. Use prophylactic antibiotics in patients with previous UTI history
Cindolo et al. [18]	f-URS	6	Neurogenic bladder patient	Recommendations to reduce sepsis: Avoid operating if evidence of UTI Administer prophylactic antibiotics if history of UTI Try to place a UAS, or at least a stent post-procedure Irrigate with caution Do not exceed 2 h of operative time, if required stage the procedure Observe patients in the first 6 post-operative hours (90% of these rare but potential lethal complications occur within 6 h)	
De La Rosette et al. [15]	URS	5	High co-morbidities (33% of patients had CVS disease and 10% had DM)	Note that URS had low complication rates, with 96% of their cohort having no complications Patients with iatrogenic ureteral strictures had higher readmission rates	
Kao and Wang [16]	f-URS	1	Low BMI, CKD, thin renal cortex patients at higher risk	Eradicate UTI prior to flexible URS Use lower irrigation pressures in patients with low BMI and CKD	
Sugihara et al. [14]	URS	8	None specified	Reduce operative duration (<90 min) Elderly and higher co-morbidities patients are more at risk of complications Perform interventions in experienced units	

Table 5 (continued)

Authors	Intervention type	Mortality number	Significant clinical parameters	Key learning point identified	Summary of key recommendations
Armitage et al. [34]	PCNL	13	Male patients at higher risk, aged 55–65 years	No recommendations	PCNL: 1. Reduce operative duration 2. Caution in patients with high stone burden 3. Aggressive treatment of pre-operative UTI and use of prophylactic antibiotics 4. Avoid forming multiple renal access tracts 5. Ensure diligent haemostasis 6. Caution in elderly patients
Baldea et al. [13]	PCNL	139	Spinal cord injury patients (matched cohort study)	Higher rates of pneumonia and sepsis in the spinal cord injury patients, resulting in higher mortality rates High UTI rates likely due to indwelling catheters, neurogenic bladder and vesicouretic reflux Recommended the treatment of pre-operative UTI, reduced operation times and aggressive pulmonary toilet	
Choi et al. [29]	PCNL	3	High stone burden patients	Reduce operative duration High stone burden patients had higher rates of complications	
Egilmez and Goren [24]	PCNL	3	High stone burden patients and higher co-morbidities	Reduce operative duration All mortalities were related to a bacteriuria or a bacteraemia Avoid forming multiple tracts to reduce the inflammatory response of the patient	
El-Nahas et al. [26]	PCNL	1	Obesity	Mortality caused by extensive bleeding which can be reduced by: Reducing operative times Avoiding the formation of renal multiple tracts Treating all pre-operative UTIs Extra caution in high stone burden patients Experienced endourologist to perform procedure	

Table 5 (continued)

Authors	Intervention type	Mortality number	Significant clinical parameters	Key learning point identified	Summary of key recommendations
Falahatkar et al. [35]	PCNL	1	Upper tract anatomical abnormalities	Caution in patients with upper tract abnormalities Avoid forming multiple renal tracts Patients with a significant post-operative haemoglobin drop had higher rates of complications	
Ghani et al. [12]	PCNL	320	High co-morbidities	Increasing age of the patient associated with higher mortality rates	
Hosseini et al. [20]	PCNL	2	Solitary kidney patients	Reduce bleeding as it may necessitate nephrectomy in severe cases. Risk factors for bleeding: Upper pole access and multiple tracts High stone burden Inexperienced surgeon Presence of single kidney	
Ibrahim et al. [37]	PCNL	2	None identified	Reduce the number of renal access tracts Higher complication rates with less experienced surgeons Reduce bleeding complications as can lead to mortality	
Knox et al. [22]	PCNL	1	Neurogenic bladder patients	Reduce the number of renal access tracts as associated with worse outcome	
Margel et al. [19]	PCNL	1	Previous surgery (open nephrolithotomy)	Reduce operative duration—especially significant in patients who had previous open renal surgery Upper pole access is associated with higher morbidity rates	
Moreno-Palacios et al. [33]	PCNL	4	Obesity	Reduce operative duration—stage procedure if necessary Treat positive urine cultures High stone burden and multiple co-morbidities are associated with increased complication rates Ensure adequate patient preparation	

Table 5 (continued)

Authors	Intervention type	Mortality number	Significant clinical parameters	Key learning point identified	Summary of key recommendations
Mousavi-Bahar et al. [21]	PCNL	1	None identified	Recommended prophylactic antibiotics for UTI Reduce risk factors for colonic injury by taking extra caution in left sided procedures, abnormal anatomy, low BMI, distended colon and elderly patients	
Oner et al. [25]	PCNL	4	None identified	Reduce operative duration Extra caution to be taken in patients with high stone burden Higher complications with less experienced surgeons	
Palnizky et al. [38]	PCNL	1	High co-morbidities	Higher pulmonary complications in younger patients which authors attributed to more aggressive treatment of fit patients	
Reddy and Shaik [36]	PCNL	1	Previous surgery (PCNL or open surgery)	Reduce operative duration Recommended pre-operative CT scan to avoid colonic injury Aim to minimalise intra-operative bleeding	
Resorlu et al. [31]	PCNL	1	Elderly patients	Higher risk of bleeding in patients with higher co-morbidities Reduce operative duration Care to be taken in patients with high stone burden	
Tefekli et al. [27]	PCNL	1	None identified	Caution in patients with high stone burden Most common complication was bleeding	
Tugcu et al. [30]	PCNL	1	Previous surgery (open surgery)	Reduce operative duration Longer operative times occurred in patients who had previous open surgery due to altered anatomy and scarring, making stone retrieval more difficult	
Unsal et al. [28]	PCNL	3	None identified	Higher risk of complications such as bleeding and death in patients with higher co-morbidities Care to be taken in elderly patients	

Table 5 (continued)

Authors	Intervention type	Mortality number	Significant clinical parameters	Key learning point identified	Summary of key recommendations
Yuruk et al. [23]	PCNL	1	High stone burden patients	Reduce operative duration Ensure care is taken in high stone burden patients Noted that patients who had previous ESWL has scattered stone fragments in their calyces which complicated PCNL	
Liu et al. [32]	Mini-PCNL	3	None identified	Diabetic patients were more at risk of developing sepsis, therefore, recommended strict control of blood glucose Increased numbers of sepsis in patients with higher stone burden and UTIs Recommendations for patients who develop septic shock: Prompt antibiotic therapy within the first hour Aggressive fluid resuscitation ITU input	
Khalaf et al. [39]	Open surgery	2	High stone burden patients (previously failed minimally invasive techniques) High number of pre-operative UTI (47.8%)	Majority of complications that occurred were bleeding Care to be taken in patients with high stone burden, anatomical abnormalities or previous stone surgery Open surgery was more common in developing countries Recommended a combined open approach with minimally invasive procedures for patients with a large stone burden and/or a more complex anatomical deformity	Open surgery: 1. Caution in patients with high stone burden 2. Ensure diligent haemostasis
Hussain et al. [8]	Multiple interventions: 113 PCNL (40.6%) 19 URS (6.8%) 146 conservative (52.6%)	29	Renal failure Rural Pakistan inhabitants Low socioeconomic class	Higher mortality rates in patients with delayed presentation and renal failure Recommend increasing public awareness to prevent delayed presentations	Multiple interventions: 1. Aggressive treatment of UTI to prevent sepsis 2. Increase public awareness to prevent delayed presentations
Pattaras et al. [10]	Multiple interventions: 18 URS (78%) 5 PCNL (22%)	1	Hepatically compromised patients (awaiting or already undergone liver transplant)	Recommend that SWL is contraindicated in patients with coagulopathies	

Table 5 (continued)

Authors	Intervention type	Mortality number	Significant clinical parameters	Key learning point identified	Summary of key recommendations
Welk et al. [11]	Multiple interventions: 27 conservative (31%) 17 SWL (19%) 30 URS (34%) 15 PCNL (17%)	6	Spinal cord injury patients	Majority of complications were related to sepsis or intraoperative cardiovascular changes Recommend yearly imaging for early detection of kidney stones so that they can be promptly managed in spinal cord injury patients	
Blackwell et al. [40]	Conservative	28	High co-morbidities	Patients who presented with sepsis had better outcomes if decompressed with a stent or nephrostomy within 48 h	Conservative: 1. Aggressive treatment of UTI 2. Prophylactic antibiotics based on previous urine culture 3. Early decompression with ureteric stent for patients presenting with sepsis
Deutsch and Subramonian [41]	Conservative	2	Very high co-morbidities (59% previously deemed unfit for surgery)	Recommended prophylactic antibiotics based on previous urine culture, as UTI is major cause of morbidity	
Kum et al. [9]	Non-specified stone mortality	1954	None identified	Identified urosepsis as a common complication of stone disease that leads to mortality Recommended prophylactic antibiotic therapy Increasing incidence of KSD	Recommended prophylactic antibiotic therapy

that sepsis is the leading cause of mortality. Similarly, recent data show the importance of keeping a low intrarenal pressure during these procedures to reduce risk of complications from sepsis and haemorrhage [44, 45].

Overall, an important take home message for urologists is the prevention sepsis in patients with KSD, which can be achieved through the use of prophylactic antibiotics in high risk patients, can reduce their mortality rates in both conservative management and for all intervention types.

Strengths and limitations

The overwhelming strength of this review is that it includes KSD mortality from all intervention-related causes, and it is the first review to collate this data. Though it gives a figure for consideration, it must be noted that three of the articles [9, 12, 13] included used national database to source their mortality rates, thus there may be a degree of overlap within their figures. As previously mentioned, one paper contributes largely to our mortality total and thus this may be an over-estimation of mortality. Despite this, all articles allowed high-risk patient categories to be identified, and as the learning points recommended by the authors are the most influential outcome of this review, these remain applicable nonetheless.

As with all systematic reviews, it must be acknowledged that there are limitations to the conclusions that are drawn. The inferences drawn are only as robust as the included articles, though reassuringly on analysis of the quality of the included studies, the majority was found to be of moderate-to-good quality. This review was, therefore, subject to publication bias that may exist in the literature. Mortality associated with KSD intervention and its conservative management is likely to have been under reported previously, due to limited reporting by urologists. The databases used to populate the datasets for these studies are user dependent, and there are urologists who may be reluctant to provide their mortality data in a voluntary setting. Additionally, though every effort was made to retrieve papers relevant to our research question, the lack of standardized terminology, keywords and MeSH terms means that we may have missed some articles that were eligible for inclusion. For future publications that include mortality data, analysis of individual cases who died and details as to the cause should be included as it provides vital information on retrospective analysis so that more robust learning outcome and recommendations can be made.

Conclusions

KSD is a pertinent healthcare issue and has been shown to have increasing mortality rates globally. This review is the first to collate the literature from the past two decades and provide a valuable insight into all-cause mortality for KSD. It was highlighted that pre-procedural optimization of the patients is key to reduce this risk and care should be taken in patients with multiple co-morbidities. Surgeons should meticulously plan for patients with high stone burden to reduce their operative time as most mortalities are procedural related. Aggressive treatment of pre-operative UTI or the use of prophylactic antibiotics has also been proven to reduce adverse events.

Author contributions LA Whitehurst: Project development, data collection, data analysis and manuscript writing; P Jones: Data collection and data analysis; BK Somani: Project development, manuscript editing.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare.

Appendix 1: Search matrix used for study

((((((((((((((((urolithiasis) OR renal stone*) OR kidney stone*) OR urinary calculi)) OR urinary stone*)) OR renal calculi)) AND life-threatening)) OR ((((((((((urolithiasis) OR renal stone*) OR kidney stone*) OR urinary calculi)) OR urinary stone*)) OR renal calculi)) AND mortality)) OR ((((((((((urolithiasis) OR renal stone*) OR kidney stone*) OR urinary calculi)) OR urinary stone*)) OR renal calculi)) AND death))) OR ((((((((ureteroscopy) AND mortality)) OR ((ureteroscopy) AND death)) OR ((ureteroscopy) AND life-threatening)) OR ((URS) AND mortality)) OR ((URS) AND life-threatening)) OR ((URS) AND death))) OR ((((((((percutaneous nephrolithotomy) AND mortality)) OR ((percutaneous nephrolithotomy) AND death)) OR ((percutaneous nephrolithotomy) AND life-threatening)) OR ((PCNL) AND mortality)) OR ((PCNL) AND death)) OR ((PCNL) AND life-threatening))) OR ((((((((shockwave lithotripsy) AND mortality)) OR ((shockwave lithotripsy) AND death)) OR ((shockwave lithotripsy) AND life-threatening)) OR ((SWL) AND mortality)) OR ((SWL) AND death)) OR ((SWL) AND life-threatening)).

(((((((((kidney stone) AND “active surveillance”)) OR ((renal stone) AND “active surveillance”)) OR ((renal calculi) AND “active surveillance”)) OR ((urinary stone) AND “active surveillance”)) OR ((urinary calculi) AND “active surveillance”)) OR ((urolithiasis) AND “active surveillance”))) OR ((((((((urolithiasis) AND “no treatment”)) OR ((urinary calculi) AND “no treatment”)) OR ((urinary stones) AND “no treatment”)) OR ((renal calculi) AND “no treatment”)) OR ((renal stones) AND “no treatment”)) OR ((kidney stones) AND “no treatment”)).

(((((((kidney stone) AND conservative)) OR ((renal stone) AND conservative)) OR ((renal calculi) AND conservative)) OR ((urinary stone) AND conservative)) OR ((urinary calculi) AND conservative)) OR ((urolithiasis) AND conservative).

References

1. Hyams ES, Matlaga BR (2014) Economic impact of urinary stones. Transl Androl Urol 3(3):278–283
2. Sorokin I, Mamoulakis C, Miyazawa K, Rodgers A, Talati J, Lotan Y (2017) Epidemiology of stone disease across the world. World J Urol 35(9):1301–1320
3. Rukin N, Siddiqui Z, Chedgy E, Somani BK (2017) Trends in upper tract stone disease in England: evidence from the hospital episodes statistics database. Urol Int 98(4):391–396
4. Sammon JD, Ghani KR, Karakiewicz PI, Bhojani N, Ravi P, Sun M, Sukumar S, Trinh VQ, Kowalczyk KJ, Kim SP, Peabody JO, Menon M, Trinh QD (2013) Temporal trends, practice patterns, and treatment outcomes for infected upper urinary tract stones in the United States. Eur Urol 64:85–92
5. Geraghty RM, Jones P, Somani BK (2017) Worldwide trends of urinary stone disease treatment over the last two decades: a systematic review. J Endourol 31(6):547–556
6. Turney BW, Reynard JM, Noble JG, Keoghane SR (2012) Trends in urological stone disease. BJU Int 109:1082–1087
7. Joanna Brigg's Institute Critical Appraisal tool. http://joannabriggs.org/research/critical-appraisal-tools.html. Accessed 21 Oct 2017
8. Hussain M, Khalique M, Khan M, Hashmi A, Hussain Z (2012) Experience with managing neglected renal calculi in a developing country. J Endourol 26:102
9. Kum F, Mahmalji W, Hale J, Thomas K, Bultitude M, Glass J (2016) Do stones still kill? An analysis of death from stone disease 1999–2013 in England and Wales. BJU Int 118:140–144
10. Pattaras JG, Ogan K, Martinez E, Nieh P (2008) Endourological management of urolithiasis in hepatically compromised patients. J Urol 179:976–980
11. Welk B, Shariff S, Ordon M, Catharine Craven B, Herschorn S, Garg AX (2013) The surgical management of upper tract stone disease among spinal cord-injured patients. Spinal Cord 51:457–460
12. Ghani KR, Sammon JD, Bhojani N, Karakiewicz PI, Sun M, Sukumar S, Littleton R, Peabody JO, Menon M, Trinh QD (2013) Trends in percutaneous nephrolithotomy use and outcomes in the United States. J Urol 190:558–564
13. Baldea KG, Blackwell RH, Vedachalam S, Kothari AN, Kuo PC, Gupta GN, Turk TMT (2017) Outcomes of percutaneous nephrolithotomy in spinal cord injury patients as compared to a matched cohort. Urolithiasis 45:501–506
14. Sugihara T, Yasunaga H, Horiguchi H, Nishimatsu H, Kume H, Ohe K, Matsuda S, Fushimi K, Homma Y (2013) A nomogram predicting severe adverse events after ureteroscopic lithotripsy: 12,372 patients in a Japanese national series. BJU International. 111:459–466
15. De La Rosette J, Denstedt J, Geavlete P, Keeley F, Matsuda T, Pearle M, Preminger G, Traxer O (2014) The clinical research office of the endourological society ureteroscopy global study: indications, complications, and outcomes in 11,885 patients. J Endourol 28:131–139
16. Kao MH, Wang CC (2016) Risk factors for developing a perirenal hematoma after flexible ureteroscopic lithotripsy. Urol Sci 27:166–170
17. Cindolo L, Castellan P, Primiceri G, Hoznek A, Cracco CM, Scoffone CM, Galfa No A, Petralia G, De Angelis M, Annino F, Malacasa E, Cormio L, Acquati P, Delorenzis E, Maugeri O, Arena G, Celia A, Giusti G, Schips L (2017) Life-threatening complications after ureteroscopy for urinary stones: survey and systematic literature review. Minerva Urol Nefrol 69:421–431
18. Cindolo L, Castellan P, Scoffone CM, Cracco CM, Celia A, Paccaduscio A, Schips L, Proietti S, Breda A, Giusti G (2016) Mortality and flexible ureteroscopy: analysis of six cases. World J Urol 34:305–310
19. Margel D, Lifshitz DA, Kugel V, Dorfmann D, Lask D, Livne PM (2005) Percutaneous nephrolithotomy in patients who previously underwent open nephrolithotomy. J Endourol 19:1161–1164
20. Hosseini MM, Yousefi A, Hassanpour A, Jahanbini S, Zaki-Abbasi M (2015) Percutaneous nephrolithotomy in solitary kidneys: experience with 412 cases from Southern Iran. Urolithiasis 43:233–236
21. Mousavi-Bahar SH, Mehrabi S, Moslemi MK (2011) Percutaneous nephrolithotomy complications in 671 consecutive patients: a single-center experience. Urol J 8:271–276
22. Knox ML, Cantor AM, Bryant JE, Burns JR (2012) Predictive factors for percutaneous nephrolithotomy outcomes in neurogenic bladder population. J Endourol 26:823–827
23. Yuruk E, Tefekli A, Sari E, Karadag MA, Tepeler A, Binbay M, Muslumanoglu AY (2009) Does previous extracorporeal shock wave lithotripsy affect the performance and outcome of percutaneous nephrolithotomy? J Urol 181:663–667
24. Egilmez T, Goren MR (2015) Fever and systemic inflammatory response syndrome seen after percutaneous nephrolithotomy: review of 1290 adult patients. J Clin Anal Med 6:196–201
25. Oner S, Okumus MM, Demirbas M, Onen E, Aydos MM, Ustun MH, Kilic M, Avci S (2015) Factors influencing complications of percutaneous nephrolithotomy: a single-center study. Urol J 12:2317–2323
26. el-Nahas AR, Eraky I, Shokeir AA, Shoma AM, el-Assmy AM, el-Tabey NA, Soliman S, Elshal AM, el-Kappany HA, el-Kenawy MR (2012) Factors affecting stone-free rate and complications of percutaneous nephrolithotomy for treatment of staghorn stone. Urology 79:1236–1241
27. Tefekli A, Karadag MA, Tepeler K, Sari E, Berberoglu Y, Baykal M, Sarilar O, Muslumanoglu AY (2008) Classification of percutaneous nephrolithotomy complications using the modified Clavien grading system: looking for a standard. Eur Urol 53:184–190
28. Unsal A, Resorlu B, Atmaca AF, Diri A, Goktug HN, Can CE, Gok B, Tuygun C, Germiyonoglu C (2012) Prediction of morbidity and mortality after percutaneous nephrolithotomy by using the Charlson Comorbidity Index. Urology. 79:55–60
29. Choi SW, Bae WJ, Ha US, Hong SH, Lee JY, Kim SW, Cho HJ (2016) Prognostic impact of stone-scoring systems after percutaneous nephrolithotomy for staghorn calculi: a single center's experience over 10 years. J Endourol 30:975–981
30. Tugcu V, Su FE, Kalfazade N, Sahin S, Ozbay B, Tasci AI (2008) Percutaneous nephrolithotomy (PCNL) in patients with previous open stone surgery. Int Urol Nephrol 40:881–884
31. Resorlu B, Diri A, Atmaca AF, Tuygun C, Oztuna D, Bozkurt OF, Unsal A (2012) Can we avoid percutaneous nephrolithotomy in high-risk elderly patients using the Charlson comorbidity index? Urology 79:1042–1047
32. Liu C, Zhang X, Liu Y, Wang P (2013) Prevention and treatment of septic shock following mini-percutaneous nephrolithotomy: a single-center retrospective study of 834 cases. World J Urol 31:1593–1597

33. Moreno-Palacios J, Maldonado-Alcaraz E, Montoya-Martinez G, Rivas-Ruiz R, Cedillo-Lopez U, Okhunov Z, Serrano-Brambila EA (2014) Prognostic factors of morbidity in patients undergoing percutaneous nephrolithotomy. J Endourol 28:1078–1084
34. Armitage JN, Withington J, van der Meulen J, Cromwell DA, Glass J, Finch WG, Irving SO, Burgess NA (2014) Percutaneous nephrolithotomy in England: practice and outcomes described in the Hospital Episode Statistics database. BJU Int 113:777–782
35. Falahatkar S, Khosropanah I, Roshan ZA, Golshahi M, Emadi SA (2009) Decreasing the complications of PCNL with alternative techniques including complete supine PCNL and subcostal approach. Pak J Med Sci 25:353–358
36. Reddy SV, Shaik AB (2016) Outcome and complications of percutaneous nephrolithotomy as primary versus secondary procedure for renal calculi. Int Braz J Urol 42:262–269
37. Ibrahim A, Elsotohi I, Mahjoub S, Elatreisy A, Soliman K, Mabrouk M, Khalaf I (2017) Factors determining perioperative complications of percutaneous nephrolithotomy: a single center perspective. Afr J Urol 23:208–213
38. Palnizky G, Halachmi S, Barak M (2014) Pulmonary complications following percutaneous nephrolithotomy: a prospective study. Curr Urol 7:113–116
39. Khalaf I, Salih E, El-Mallah E, Farghal S, Abdel-Raouf A (2013) The outcome of open renal stone surgery calls for limitation of its use: a single institution experience. Afr J Urol 19:58–65
40. Blackwell RH, Barton GJ, Kothari AN, Zapf MAC, Flanigan RC, Kuo PC, Gupta GN (2016) Early intervention during acute stone admissions: revealing "the weekend effect" in urological practice. J Urol 196:124–130
41. Deutsch PG, Subramonian K (2016) Conservative management of staghorn calculi: a single-centre experience. BJU Int 118:444–450
42. Türk C, Petřík A, Sarica K, Seitz C, Skolarikos A, Straub M, Knoll T (2016) EAU guidelines on interventional treatment for urolithiasis. Eur Urol 69:475–482
43. Breda A, Angerri O (2014) Retrograde intrarenal surgery for kidney stones larger than 2.5 cm. Curr Opin Urol 24:179–183
44. Osther PJS (2018) Risks of flexible ureterorenoscopy: pathophysiology and prevention. Urolithiasis 46(1):59–67
45. Loftus CJ, Hinck B, Makivey I et al (2018) Mini versus standard percutaneous nephrolithotomy: the impact of sheath size on intrarenal pelvic pressure and infectious complications in a porcine model. J Endourol. https://doi.org/10.1089/end.2017.0602 **(epub ahead of print)**